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Clinical outcomes and safety of the immune checkpoint inhibitor rechallenge in Hodgkin lymphoma: an off-trial analysis

Running Title: ICI rechallenge in Hodgkin lymphoma

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Abstract

Immune checkpoint inhibitors (ICIs) are effective in classical Hodgkin lymphoma (cHL), but immune-related adverse events (irAEs) may lead to treatment interruption in some patients. We conducted a retrospective cohort study of 145 patients with cHL treated with ICIs between 2015 and 2024. Cohort 1 included 130 patients in which 15 received ICI rechallenge within the same treatment line following irAE-related interruption and 115 who did not undergo rechallenge. Another 15 patients who underwent ICI rechallenge in a subsequent line of therapy comprised cohort 2. In cohort 1, PFS and DOR did not differ between rechallenged and non-rechallenged patients (HR 1.7, 95% CI 0.31–9.3, p = 0.55; HR 2.7, 95% CI 0.24–31.2, p = 0.42, respectively). Recurrent irAEs occurred in 20%, with recurrence of the same irAE in 7% in cohort 1. In cohort 2, 53% had refractory disease, whereas 47% responded to initial ICI and were subsequently rechallenged at progression. The median PFS was 7.4 months (95% CI: 5.0–NE) and 13.5 months (95% CI 8.1–46.7), respectively. ICI rechallenge after irAE-related interruption was feasible in selected patients.

Introduction

Classical Hodgkin lymphoma (cHL) is a malignancy characterized by the presence of Reed–Sternberg cells within an immunologically active tumor microenvironment[1]. A hallmark of cHL biology is the frequent amplification of chromosome 9p24.1, resulting in the overexpression of programmed death-ligand 1 (PD-L1) and PD-L2. This biology makes cHL particularly susceptible to immune checkpoint inhibitors (ICIs)[2-5]. PD-1 blockade is now a standard treatment option for both in frontline and in relapsed or refractory (R/R) setting in cHL[6-8]. Because some patients discontinue ICI due to adverse events (AEs), the safety and efficacy of ICI rechallenge after interruption due to immune-related adverse events (irAEs) is a clinically relevant question.

Despite increasing clinical use of ICI rechallenge in cHL, high-quality evidence remains limited. A recent systematic review suggests that rechallenge can produce meaningful responses with an acceptable toxicity profile in relapsed/refractory (R/R) cHL[9]. However, available data are largely retrospective, small, and clinically heterogeneous. We therefore conducted a retrospective study addressing two complementary questions. First, we evaluated the safety and clinical outcomes of same-line ICI rechallenge after irAE-related interruption. Second, we characterized outcomes after subsequent-line ICI rechallenge in patients with disease refractory to initial ICI or relapse following an initial response.

Methods

Study Design and Setting

This retrospective cohort study was conducted at Mayo Clinic, a tertiary academic medical center in the United States. We reviewed electronic health records of patients diagnosed with

cHL who received ICIs between January 1, 2015, and December 31, 2024. ICI rechallenge was defined as re-exposure to an ICI after discontinuation of a prior ICI course. Details of the methods are described in **Table S1**. The primary analysis evaluated patients who resumed ICI after temporary interruption for irAEs within the same treatment line and compared them with the remaining patients in cohort 1. Propensity score matching (PSM) was performed for the primary analysis using 1:3 nearest-neighbor matching with replacement and a caliper of 0.2 on the logit of the propensity score. Prior autologous stem cell transplant before initial ICI exposure and the Hasenclever International Prognostic Score (IPS) were included in the model. The comparator group comprised 115 patients who did not undergo ICI rechallenge. Among them, 109 had completed or discontinued their initial ICI course because of progression, irAEs, treatment completion, or planned autologous stem cell transplantation, whereas six remained on their initial ICI at data cutoff. Patients who underwent ICI rechallenge after transition to a subsequent treatment line were excluded from the primary comparison and analyzed separately as cohort 2. We performed two exploratory descriptive analyses: (1) a subgroup analysis of patients with R/R cHL within cohort 1 who received ICI as second-line or later, discontinued treatment because of irAEs, and were or were not later rechallenged; and (2) an analysis of patients in cohort 2 who received ICI rechallenge in a subsequent line of therapy after disease refractory to initial ICI or after relapse following an initial response to ICI. Rechallenge could occur with the same PD-1 inhibitor or with a different agent in the same class.

Study Population and Data Sources

Eligible patients were adults (≥18 years) with a histologically confirmed diagnosis of cHL who received at least one cycle of ICI therapy. Patients receiving ICI therapy for both frontline and

R/R settings were eligible. Initial ICI exposure included both monotherapy and combination regimens. Patients were identified through institutional electronic health records using diagnostic and treatment codes. To be included in the rechallenge cohort, patients were required to receive a second course of ICI therapy after discontinuation of the initial ICI.

Definitions and Outcome Measures

The primary outcomes for cohort 1 were progression-free survival (PFS) and duration of response (DOR). Index dates were defined separately for each analysis. For the primary matched analysis, PFS and OS were measured from the last dose of the relevant ICI course (the last dose of the rechallenge course for rechallenged patients and the last dose of the initial ICI course for non-rechallenged patients) to minimize immortal time bias since rechallenged patients necessarily survived to re-exposure, and anchoring at first ICI exposure would have introduced event-free time for the rechallenged group. DOR was measured from the first documented response to the initial ICI. For exploratory analysis 1, time to progression was measured from the date of ICI discontinuation because of the index irAE. For cohort 2, PFS and EFS were measured from the first dose of the rechallenge ICI, whereas DOR was measured from the first documented response after rechallenge. PFS was defined as the time from this index date to progression or death, whichever came first[10, 11]. DOR was defined as the time from the first recorded response to the first ICI based on positron emission tomography–computed tomography (PET-CT) until progression. Event-free survival (EFS) for cohort 2 was defined as the time from the first dose of ICI rechallenge to the first occurrence of disease progression, treatment discontinuation because of an AE, initiation of another systemic treatment for a reason other than an AE, or death. Response was assessed from clinical and PET-CT findings using the Lugano

classification[12]. irAEs were identified by chart review, attributed by the treating clinicians, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Events were categorized by organ system and by whether they represented recurrence of the same type irAE. Response categories included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).

The Ethics approval and the Patient consent

The study was approved by the Mayo Clinic Institutional Review Board as a retrospective medical-records study (IRB No. 25-008536) and was conducted in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived by the institutional review board because this retrospective study involved minimal risk and used existing clinical data.

Results

Patient Characteristics

The groups and flow of the included patients are shown in **Figure S1**. Cohort 1 comprised 130 patients, including 15 who later rechallenged ICI after temporary interruption because of irAEs. Among the remaining 115 patients in cohort 1, 109 had completed or discontinued their initial ICI course and six remained on treatment at data cutoff. For the 109 patients whose initial ICI course was not later resumed, the reasons included progression, irAEs, treatment completion, and planned autologous stem cell transplant. For time-to-event analyses within cohort 1, 4/15 rechallenged patients and 6/115 patients who had not later rechallenged ICI were still receiving

ICI at data cutoff and were excluded. To address a clinically relevant scenario, we also identified an exploratory subgroup of 13 patients with R/R cHL within cohort 1 who received ICI as second-line or later therapy and discontinued treatment because of irAEs to assess response and outcomes specifically in the R/R setting; nine were subsequently rechallenged and four were not. Cohort 2 included 15 patients who underwent ICI rechallenge in a subsequent line of therapy after prior ICI exposure. All 15 had received their initial ICI in the R/R setting: eight had disease refractory to initial ICI and were rechallenged with a different ICI, whereas seven had achieved CR or PR to initial ICI and were rechallenged at relapse (six with the same ICI and one with a different ICI).

Baseline characteristics of the patients in the cohort 1 are summarized in **Table 1**. Initial ICI regimen composition, including monotherapy and combination regimens, is summarized in **Table 2**. The median age at diagnosis was 41 years (IQR: 26–66), and 41% of patients were female. 92% were White with an ECOG performance status of 0–1 in 95%. The distribution of age and disease stage was similar between groups, although a trend was observed for a higher proportion of rechallenged patients receiving autologous stem cell transplantation prior to initial ICIs (47% vs. 21%, $p = 0.07$). Median follow-up duration for the entire cohort was 40.6 months overall (IQR: 20.5–75.4); 45.1 months (IQR: 18.8–80.4) in the rechallenged cohort and 40.6 months (IQR: 21.2–74.7) in the non-rechallenged cohort ($p = 0.32$). In the primary analysis, nine rechallenged patients were matched to 25 controls (mean 2.8 controls per rechallenged patient). In the matched cohort, prior autologous transplantation before ICI had been performed in 33% of rechallenged patients and 36% of non-rechallenged controls. Autologous transplantation after ICI was performed in 22% of rechallenged patients and 20% of non-rechallenged controls. Initial

ICI was administered in the R/R setting in 67% of rechallenged patients and 72% of non-rechallenged controls, respectively. The median number of ICI cycles was 8 (IQR, 3–17) among patients who subsequently underwent rechallenge and 6 (IQR, 4–12) among patients who did not undergo rechallenge ($p = 0.98$). In the propensity-score–matched cohort, the median number of ICI cycles was 6 (IQR, 3–15) and 6 (IQR, 4–26), respectively ($p = 0.50$). Details of baseline balance in the matched cohort are summarized in **Table S2** and **Figure S2**.

Immune-related Adverse Events

During the initial ICI course in cohort 1, 31/130 (24%) experienced irAEs (**Table 2**). The frequency of irAEs did not differ according to whether initial ICI was administered in the frontline or R/R setting (11/48 [22.9%] vs 20/82 [24.4%]; p=0.84). Most irAEs were of grade 1–2, and eight (26%) experienced grades ≥3 irAEs. There was no difference in the severity of irAE between the rechallenged and non-rechallenged groups. The distribution of index irAE types differed between rechallenged and non-rechallenged patients, although numbers were small and these comparisons were exploratory. Among the 15 patients who underwent ICI rechallenge after irAE-related discontinuation, nine held ICI after the index irAE without immunosuppressive treatment, whereas six had initially required prednisone 1 mg/kg. At the time of rechallenge, three of the six patients remained on prednisone at 10 mg/day, 30 mg/day, or 50 mg/day whereas the remaining 12 rechallenged patients were not receiving prednisone. Recurrent irAEs occurred in three of the 15 patients (20%), including pneumonitis (n = 2) and hepatitis (n = 1) (**Table 3**). None of the five patients with a grade 1 index irAE experienced a recurrent irAE, whereas recurrent irAEs occurred in two of six patients with a grade 2 index irAE and one of four patients

with a grade 3 index irAE. Two of the three patients who were on prednisone upon ICI rechallenge had recurrent irAEs. Recurrence of the same irAE type occurred in one (7%; grade 3 hepatitis). Overall, 12/15 rechallenged patients (80%) did not experience an irAE during the second ICI course. Patient-level details are shown in **Table 4**.

Outcomes

Primary Analysis

We performed the primary analysis to evaluate whether ICI rechallenge after temporary discontinuation due to irAEs affected outcomes. In cohort 1, the study group comprised 15 patients who later resumed ICI after irAE-related interruption, whereas the comparator group comprised 115 patients who did not undergo ICI rechallenge. Response data are summarized in **Tables 2 and 3**. The overall response rate (ORR) for the initial ICI course was 80% in the rechallenge group and 77% in the no-rechallenge group, with no significant difference between groups ($p = 0.77$). The median interval from initial ICI discontinuation to rechallenge was 5.0 months (IQR 2.4–15.4). In the PSM cohort, ICI rechallenge was not associated with a difference in PFS (HR 1.7, 95% CI 0.31–9.3; $p = 0.55$; **Figure 1**) or DOR (HR 2.7, 95% CI 0.24–31.2; $p = 0.42$; **Figure 2**) compared with no rechallenge. Median OS from the last ICI exposure was not reached in either group, and OS did not differ between groups ($p = 0.48$; **Figure S3**). Unadjusted analyses were directionally consistent with the matched analyses (**Figure S4A-B**). When stratified by the setting of initial ICI exposure, the R/R subgroup showed no statistically significant PFS difference between rechallenged and non-rechallenged patients (HR, 1.8; 95% CI, 0.41–8.3; p=0.43; **Figure S5A**). In the non-R/R subgroup, there were only three rechallenged

patients, precluding a reliable comparative HR estimate (**Figure S5B**). In the sensitivity analysis restricted to patients who discontinued ICI because of an irAE, no statistically significant PFS difference was observed between rechallenged and non-rechallenged patients (HR, 0.79; 95% CI, 0.13–4.8; p=0.80; **Figure S5C**).

Exploratory analysis 1

To examine the clinically specific scenario of R/R cHL patients within cohort 1 who received ICI as second-line or later and discontinued treatment because of irAEs, we analyzed 13 patients within cohort 1; nine were later rechallenged and four were not. The clinical characteristics, including the index irAE type and grade, timing of ICI discontinuation, and subsequent treatment course, are summarized in **Table S3**. Among the nine rechallenged patients, the median interval from ICI discontinuation to rechallenge was 10.3 months (IQR 4.5–20.2), and recurrent irAE occurred in two patients. Best response after ICI rechallenge was CR in five, PR in one, SD in one, and PD in two. Among the four patients who were not rechallenged, reasons for non-rechallenge included sustained remission after irAE-related discontinuation (patients 10 and 11), alternate therapy (patient 12), and clinician choice (patient 13) (**Table S3**).

Exploratory analysis 2

Cohort 2 included 15 patients who underwent ICI rechallenge in a subsequent line of therapy after prior ICI exposure. The details of the patients are described in **Table S4**. None of the 15 patients in cohort 2 received ICI as frontline therapy; four had refractory disease from the

treatment before the initial ICI treatment. Eight patients had disease refractory to initial ICI and were rechallenged with a different ICI. At the time of ICI rechallenge, treatment composition in cohort 2 included single-agent ICI (n = 7; 47%), ICI with brentuximab vedotin (n = 1; 7%), and combination of ICI with chemotherapy (n = 7; 47%). The median treatment line at rechallenge ICI initiation in this subgroup was 3 (IQR 3–11). The best response to rechallenge was CR in three, PR in two, and PD in three, corresponding to an ORR of 62.5%. Median PFS from rechallenge was 7.4 months (95% CI 5.0–NE) (**Figure S6A**), and median EFS was 6.3 months (95% CI 4.2–NE) (**Figure S6B**). The DORs among the three patients with CR were 1.9, 25.7, and 28.1 months; one died of a non-lymphoma-related cause. The remaining seven patients in cohort 2 had responses to the initial ICIs and were rechallenged upon relapse. The seven patients achieved CR or PR to their initial ICI and were rechallenged at relapse. Six received the same ICI and one received a different ICI. Best response to rechallenge was CR in six and PD in one, corresponding to an ORR of 85.7%. Median PFS from rechallenge was 13.5 months (95% CI 8.1–46.7) **(Figure S7A**), and median EFS was 13.5 months (95% CI 2.7–46.7) (**Figure S7B**).

Discussion

In this retrospective off-trial cohort study, ICI rechallenge after irAE-related interruption within the same treatment line was not associated with inferior PFS, DOR, or OS in the matched primary analysis. Recurrent irAEs after rechallenge were seen in 20%, and recurrence of the same irAE type occurred in 7% of the patients. These data support ICI rechallenge as a reasonable option for carefully selected patients with cHL whose initial ICI course was interrupted because of toxicity. The observation that ICI rechallenge was not associated with inferior survival outcomes aligns with prior studies suggesting that selected patients may derive

durable responses from re-exposure to ICIs[9, 13, 14]. In particular, the absence of an apparent PFS decrement despite treatment interruption suggests that rechallenge may preserve disease control in selected patients. Although it requires further validation with a large prospective cohort, our exploratory subsequent-line analyses suggest that benefit derived from ICI rechallenge may depend on prior ICI sensitivity based on the results of the exploratory analyses.

Prior reports have shown grade ≥3 AE rates of 21% in pooled R/R cHL trials, and 33% in the frontline nivolumab-AVD setting[8, 15]. In our cohort, recurrent irAEs after rechallenge occurred in 3/15 (20%), and only one (7%) experienced recurrence of the same irAE type. These findings support the safety of rechallenge in selected patients, and are consistent with prior off-trial evidence suggesting that prior irAEs do not preclude future immunotherapy[13, 14, 16].

In clinical practice, the decision to pursue rechallenge should account for the prior response, the reason for discontinuation, the extent of irAEs, and the current disease status. Despite the limited sample sizes, the present data suggest that patients with disease refractory to initial ICI may derive limited PFS benefit from rechallenge (**Figure S6**). In such patients, alternative treatment strategies may need to be considered. In contrast, patients who initially responded to ICIs can be considered for rechallenge upon relapse, especially when other treatment options are limited. To help predict who may benefit from ICI rechallenge, future studies should aim to define predictive biomarkers of response and toxicity. A previous study including 470 patients with various cancers, predominantly solid tumors but including 37 patients with hematologic malignancies, showed that lower neutrophil-to-lymphocyte ratio, monocyte-to-lymphocyte ratio, and platelet-to-lymphocyte ratio were identified to be associated with a higher likelihood of irAEs and better

OS in patients treated with ICIs[17]. As irAEs are considered mostly T-cell driven, elevated interferon-inducible T-cell alpha chemoattractant was also associated with irAE occurrence in R/R cHL patients[18]. However, no single reliable biomarker has been found to be of utility in a routine clinical setting, which is an area for future research.

Several limitations should be acknowledged. First, the retrospective design introduces risks of selection bias and unmeasured confounding. Second, although the median number of ICI cycles was not significantly different between groups in either the full or matched cohorts, there was patient-level variation in treatment duration. The primary matched analysis began at the last dose of the relevant ICI course and therefore evaluated disease-control durability after completion or discontinuation of that course. Differences in individual treatment duration, response status at the end of therapy, and clinical selection for rechallenge may nevertheless have limited comparability. Third, the sample size was limited across the analyses, particularly in the exploratory subgroups. The R/R subgroup within cohort 1 who received ICI as second-line or later and discontinued treatment because of irAEs included only 13 patients, precluding robust comparative inference. Next, treatment decisions, including whether to discontinue or later resume ICI, were not standardized and may have reflected clinician judgment, toxicity resolution, tempo of disease progression, and treatment availability. Although corticosteroid exposure at the time of rechallenge was reviewed, only three patients were receiving prednisone at rechallenge, which precluded meaningful assessment of whether concurrent corticosteroid use influenced irAE recurrence or treatment efficacy. Finally, the cohort remained heterogeneous with respect to treatment setting and prior therapy exposure despite efforts to examine more clinically restricted subgroups.

In conclusion, ICI rechallenge after irAE-related interruption in cHL was associated with 20% recurrent irAE rates and was not associated with inferior PFS, DOR, or OS in the matched primary analysis in the present cohorts. Exploratory data further suggest that the degree of benefits from ICI rechallenge may differ based on sensitivity to prior ICI exposure. Prospective studies are needed to define which patients are most likely to benefit from rechallenge.

References

1. Alibrahim MN, Gloghini A, Carbone A. Classic Hodgkin lymphoma: pathobiological features that impact emerging therapies. Blood Rev. 2025;71:101271.
2. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2015;372(4):311-319.
3. Chen R, Zinzani PL, Fanale MA, et al. Phase II study of the efficacy and safety of pembrolizumab for relapsed/refractory classic Hodgkin lymphoma. J Clin Oncol. 2017;35(19):2125-2132.
4. Song Y, Gao Q, Zhang H, et al. Tislelizumab for relapsed/refractory classical Hodgkin lymphoma: 3-year follow-up and correlative biomarker analysis. Clin Cancer Res. 2022;28(6):1147-1156.
5. Wu J, Song Y, Chen X, et al. Camrelizumab for relapsed or refractory classical Hodgkin lymphoma: Extended follow-up of the multicenter, single-arm, Phase 2 study. Int J Cancer. 2022;150(6):984-992.
6. Ansell SM, Bröckelmann PJ, von Keudell G, et al. Nivolumab for relapsed/refractory classical Hodgkin lymphoma: 5-year survival from the pivotal phase 2 CheckMate 205 study. Blood Adv. 2023;7(20):6266-6274.
7. Armand P, Zinzani PL, Lee HJ, et al. Five-year follow-up of KEYNOTE-087: pembrolizumab monotherapy for relapsed/refractory classical Hodgkin lymphoma. Blood. 2023;142(10):878-886.
8. Herrera AF, LeBlanc M, Castellino SM, et al. Nivolumab+AVD in advanced-stage classic Hodgkin’s lymphoma. N Engl J Med. 2024;391(15):1379-1389.
9. Nishimura Y, Han Y, Toumeh N, et al. Outcomes of immune checkpoint inhibitor rechallenge in relapsed and/or refractory Hodgkin lymphoma. Blood Neoplasia. 2025;2(3):100134.
10. Inomata M, Matsumoto M, Hayashi K, et al. Association between the severity of immune-related adverse events and the prognosis in patients with non-small cell lung cancer receiving treatment with immune checkpoint inhibitors. Anticancer Res. 2023;43(7):3241-3246.
11. Hernán MA, Sauer BC, Hernández-Díaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. J Clin Epidemiol. 2016;79:70-75.
12. Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol. 2014;32(27):3059-3068.
13. Dolladille C, Ederhy S, Sassier M, et al. Immune checkpoint inhibitor rechallenge after immune-related adverse events in patients with cancer. JAMA Oncol. 2020;6(6):865-871.
14. Plazy C, Hannani D, Gobbini E. Immune checkpoint inhibitor rechallenge and resumption: a systematic review. Curr Oncol Rep. 2022;24(9):1095-1106.
15. Zhang X, Chen L, Zhao Y, Yin H, Ma H, He M. Safety and efficacy in relapsed or refractory classic Hodgkin's lymphoma treated with PD-1 inhibitors: a meta-analysis of 9 prospective clinical trials. Biomed Res Int. 2019;2019:9283860.
16. Bylsma S, Yun K, Patel S, Dennis MJ. Immune checkpoint inhibitor rechallenge after prior immune toxicity. Curr Treat Options Oncol. 2022;23(9):1153-1168.
17. Michailidou D, Khaki AR, Morelli MP, Diamantopoulos L, Singh N, Grivas P. Association of blood biomarkers and autoimmunity with immune related adverse events in patients with cancer treated with immune checkpoint inhibitors. Sci Rep. 2021;11(1):9029.

18. Luke N, Pratt M, Gong J, Borghi S, Diefenbach CS, Hillier K. Predictive cytokine biomarkers for immune-related adverse events associated with immune checkpoint inhibitor therapy in Hodgkin lymphoma. J Clin Oncol. 2024;42(16_suppl):e14651.

Table 1. Characteristics of Included Patients

	Overall N= 130 n (%)	Rechallenge N=15 n (%)	No Rechallenge N=115 n (%)	*p*-Value
Age (Years)	41 (26–66)	39 (27–70)	41 (25–65)	0.50
Female	53 (41)	8 (53)	45 (39)	0.30
Ethnicity				
White	119 (92)	15 (100)	104 (90)	0.42
ECOG PS				0.92
0-1	123 (95)	14 (93)	109 (95)	
2-3	7 (5)	1 (7)	6 (5)	
Stage				0.50
I-II	49 (38)	4 (27)	45 (39)	
III	31 (24)	3 (20)	28 (24)	
IV	50 (38)	8 (53)	42 (37)	
Histological Subtype				0.05
NS	90 (69)	12 (80)	78 (68)	
Mixed	19 (15)	2 (13)	17 (15)	
Others	3 (2)	1 (7)	2 (2)	
Not documented	18 (14)	0	18 (16)	
IPS	2 (1–3)	3 (1–5)	2 (1–3)	0.09
Initial ICI in the R/R setting	82 (63)	11 (73)	71 (62)	0.37
Number of ICI cycles	6 (4–12)	8 (3–17)	6 (4–12)	0.98
Follow-up Periods (month, IQR)	40.6 (20.5-75.4)	45.1 (18.8-80.4)	40.6 (21.2-74.7)	0.32
Prior lines of Therapy before ICI (median, IQR)	1 (0-2)	1 (0-4)	1 (0-2)	0.26
0	48 (37)	4 (27)	44 (38)	
1	34 (26)	5 (33)	29 (25)	
2+	48 (37)	6 (40)	42 (37)	
BV prior to ICI	54 (42)	8 (53)	46 (40)	0.45
Auto-SCT prior to ICI	31 (24)	7 (47)	24 (21)	0.07
Auto-SCT after ICI	30 (23)	2 (13)	28 (24)	0.52

Abbreviations: Auto-SCT, autologous stem cell transplant; BV, brentuximab vedotin; ECOG PS, performance status; ICI, immune checkpoint inhibitor; IPS, Hasenclever International Prognostic Score; R/R, relapsed or refractory

Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as median (IQR).

Table 2. Details of 1st Immune Checkpoint Inhibitor Treatment and Adverse Events

	Overall N= 130 n (%)	Rechallenge N=15 n (%)	No Rechallenge N=115 n (%)	*p*-Value*
Type of 1st ICI				0.54
Nivolumab	77 (59)	7 (47)	70 (61)	
Pembrolizumab	53 (41)	8 (53)	45 (39)	
Details of Treatment				0.121
ICI monotherapy	51 (39)	9 (60)	42 (37)	
ICI + BV	20 (15)	0	20 (17)	
ICI + chemotherapy	59 (45)	6 (40)	53 (46)	
Response				0.008
CR	90 (69)	12 (80)	78 (68)	
PR	10 (8)	0	10 (9)	
SD	8 (6)	3 (20)	5 (4)	
PD	22 (17)	0	22 (19)	
ORR	100 (77)	12 (80)	88 (77)	0.77
Reason for ICI discontinuation*				<0.0001
Progression	21 (16)	0	21 (18)	
AEs	25 (19)	15 (100)	10 (9)	
Treatment completion	58 (45)	0	58 (50)	
Planned Auto-SCT	17 (13)	0	17 (15)	
Others	3 (2)	0	3 (3)	
Types of irAEs**				<0.0001
Hepatitis	6 (5)	4 (27)	2 (2)	
Thyroiditis	5 (4)	0	5 (4)	
Colitis	3 (2)	1 (7)	2 (2)	
Pneumonitis	1 (1)	1 (7)	0	
Others	16 (12)	9 (60)	7 (6)	
irAE Grade				0.57
1	8 (26)	5 (33)	3 (19)	
2	15 (48)	6 (40)	9 (56)	
3	7 (23)	4 (27)	3 (19)	
4	1 (3)	0	1 (6)	

Abbreviations: AE, adverse events; Auto-SCT, autologous stem cell transplant; CR, complete response; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; ORR, objective response rate; PD, progressive disease; PR, partial response; SD, stable disease

Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as median (IQR).

*For categorical variables, *p*-values compare the rechallenge and no-rechallenge groups within cohort 1; for the response variable, the *p*-value reflects comparison of the overall CR/PR/SD/PD distribution. Six non-rechallenged patients remained on their initial ICI at the time of data cut off. All rechallenged patients discontinued ICIs due to AEs by definition.

**Thirty-one patients experienced irAEs.

Table 3. Details of ICI Rechallenges

	Rechallenge N= 15 n (%)
Type of 2nd ICI	
Nivolumab	10 (67)
Pembrolizumab	5 (33)
Time until rechallenge (month, IQR)	5.0 (2.4-15.4)
Response	
CR	9 (60)
PR	2 (13)
SD	2 (13)
PD	2 (13)
Types of irAEs	
Pneumonitis	2 (13)
Hepatitis	1 (7)
None	12 (80)
Recurrence of the same irAE type*	1 (7)
irAE Grade	
1	0
2	0
3	1 (7)
4	2 (13)

Abbreviations: AE, adverse events; CR, complete response; ICI, immune checkpoint inhibitor; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease

Data are presented as n (%) unless otherwise indicated. Continuous variables are presented as median (IQR).

*One patient experienced recurrence of the same irAE type (grade 3 hepatitis).

Table 4. Clinical details of the 15 rechallenged patients

Patient No./Age/Sex	ICI agent	*Index irAE type/grade*	*Time to discontinuation (month)*	*Time from discontinuation to rechallenge (month)*	*Initial ICI response*	*Interventions for irAE*	*Rechallenge with same ICI (Y or N)*	*Recurrent irAE/type/grade*	*Prednisone-equivalent dose on rechallenge*	*Rechallenge ICI response*
1/26/M	P	Ocular myositis/1	6.3	8.5	CR	ICI DC + Prednisone	Y	N	10 mg/day	CR
2/39/M	N	IRR/1	0.70	24.8	CR	ICI DC	Y	N	None	PD
3/39/F	P	Pneumonitis/2	13.8	15.4	CR	ICI DC + Prednisone	Y	N	None	CR
4/54/M	N	Hepatitis/2	0.78	3.0	SD	ICI DC	Y	N	None	PR
5/77/F	P	Pancreatitis/2	1.5	46.3	CR	ICI DC	Y	Y/Pneumonitis/4	None	CR
6/39/M	N	Colitis/2	10.5	15.6	CR	ICI DC + Prednisone	Y	N	None	PD
7/21/F	P	Aseptic meningitis/1	0.60	1.2	CR	ICI DC	Y	N	None	CR
8/27/F	N	Pleuritis/2	18.7	10.0	CR	ICI DC + Prednisone	Y	Y/Pneumonitis/4	30 mg/day	SD
9/66/M	P	Nephritis/3	0.70	6.0	SD	ICI DC	Y	N	None	CR
10/68/M	P	Nephritis/1	7.5	2.5	CR	ICI DC	N	N	None	CR
11/81/F	N	Hepatitis/3	0.70	4.3	CR	ICI DC	Y	N	None	SD
12/72/F	N	Hepatitis/3	2.8	2.6	CR	ICI DC + Prednisone	Y	Y/hepatitis/3	50 mg/day	CR
13/70/F	P	Dermatitis/2	0.70	0.70	SD	ICI DC	N	N	None	PR
14/24/M	N	Hepatitis/3	2.4	4.0	CR	ICI DC + Prednisone	Y	N	None	CR
15/29/F	P	IRR/1	0.70	0.80	CR	ICI DC	N	N	None	CR

Abbreviations: AIHA, autoimmune hemolytic anemia; CR, complete response; DC, discontinuation; ICI, immune checkpoint inhibitor; IRR, infusion-related reaction; irAE, immune-related adverse event; N/A, not applicable; N, nivolumab; P, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

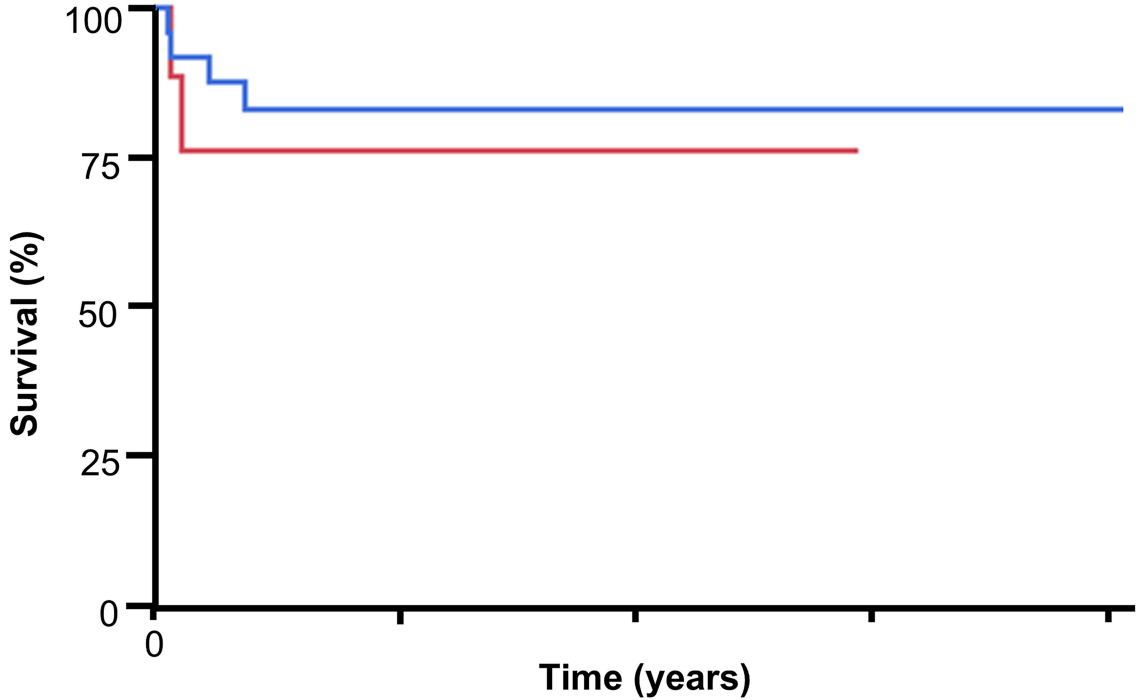
Figure Legends

Figure 1. Progression-free survival in the propensity-score matched cohorts using autologous stem cell transplant status and the Hasenclever International Prognostic Score

Abbreviations: NR, not reached; PFS, progression-free survival; RC, rechallenge

Figure 2. Duration of response in the propensity-score matched cohorts

Abbreviations: DOR, duration of response; NR, not reached; RC, rechallenge

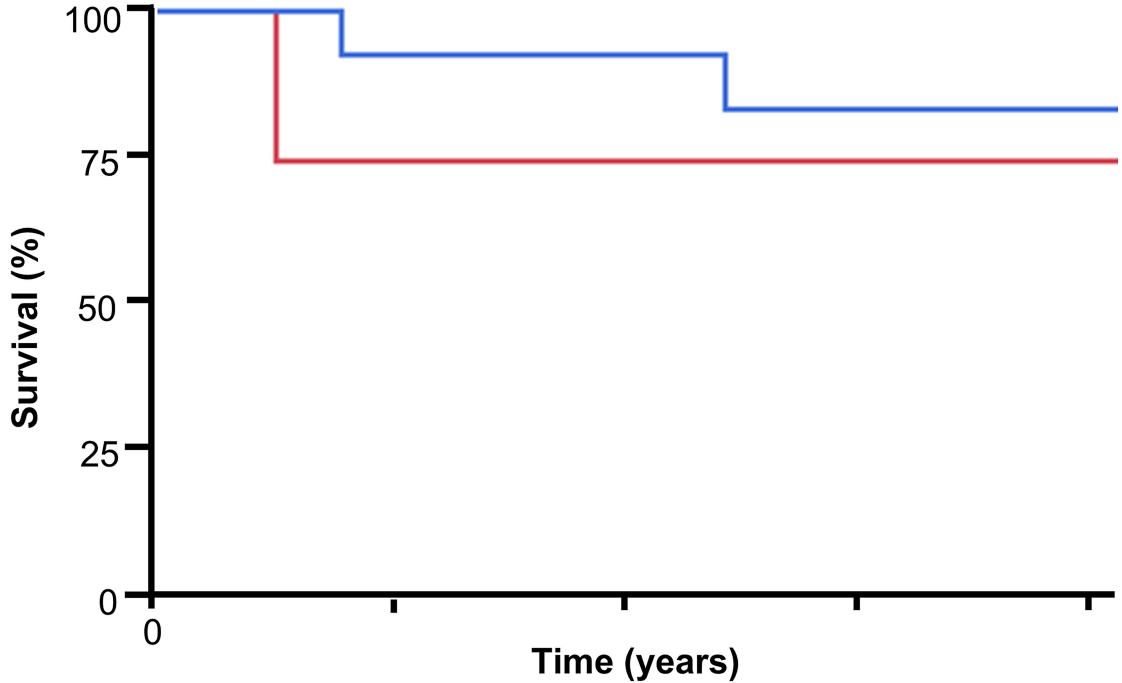


RC
No RC

Group	Hazard ratio (95% CI)	P-value
No RC	Reference	
RC	1.7 (0.31-9.3)	0.55

Group	2-year PFS
No RC	83.2%
RC	76.2%

No. at Risk	0		1		2		3		4
1. RC	9	4	4	3	3	1	0	0	0
2. No RC	25	18	15	11	10	13	7	7	5



RC
No RC

Group	Hazard ratio (95% CI)	P-value
No RC	Reference	
RC	2.7 (0.24-31.2)	0.42

Group	3-year DOR
No RC	83.6%
RC	75.0%

No. at Risk	0		1		2		3		4
1. RC	6	4	3	1	1	1	1	1	1
2. No RC	16	15	13	12	11	9	5	5	4

Appendix

The efficacy and safety of the immune checkpoint inhibitor rechallenge in Hodgkin lymphoma

Yoshito Nishimura, Joey Maiocco, Guneet Janda, Adrienne Nedved, Yiqun Han, Urshila Durani, Grzegorz S. Nowakowski, Jonas Paludo, Gita Thanarajasingam, Ivana Micallef, Patrick Johnston, Thomas E. Witzig, Thomas Habermann, Matthew Maurer, Philippe Armand, Stephen M. Ansell, Jithma Abeykoon

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Abbreviations are defined in each table and figure.
This supplementary material has been provided by the authors to give readers additional information about their work.

Table S1. Detailed Methods

Study Design and Setting	The primary analysis evaluated patients who resumed ICI after temporary interruption for irAEs within the same treatment line and compared them with the remaining patients in cohort 1. The comparator group comprised 115 patients who did not undergo ICI rechallenge. Among them, 109 had completed or discontinued their initial ICI course because of progression, irAEs, treatment completion, planned autologous stem cell transplantation, or other reasons, whereas six remained on their initial ICI at data cutoff. Patients who underwent ICI rechallenge after transition to a subsequent treatment line were excluded from the primary comparison and analyzed separately as cohort 2. We performed two exploratory descriptive analyses: (1) a subgroup analysis of patients with R/R cHL within cohort 1 who received ICI as second-line or later, discontinued treatment because of irAEs, and were or were not later rechallenged; and (2) an analysis of patients in cohort 2 who received ICI rechallenge in a subsequent line of therapy after disease refractory to initial ICI or after relapse following an initial response to ICI. Rechallenge could occur with the same PD-1 inhibitor or with a different agent in the same class.
Study Population and Data Sources	Eligible patients were adults (≥18 years) with a histologically confirmed diagnosis of cHL who received at least one cycle of ICI therapy. Patients receiving ICI therapy for both frontline and R/R settings were eligible. Initial ICI exposure included both monotherapy and combination regimens. Patients were identified through institutional electronic health records using diagnostic and treatment codes. To be included in the rechallenge cohort, patients were required to receive a second course of ICI therapy after discontinuation of the initial ICI. The control cohort comprised patients who discontinued ICI without subsequent rechallenge during the same study period. We excluded 28 patients with insufficient medical records or without pathological confirmation of cHL. Demographic, clinical, and treatment-related data, including age, sex, disease stage, disease status (R/R or not), the number of ICI cycles given, performance status, ICI regimen, response to therapy, information about AEs, and prior treatment and transplant history, were extracted via chart review. For rechallenged patients, we additionally abstracted management of the index irAE after ICI interruption, and whether immunosuppressive therapy was still being administered at the time of ICI rechallenge.

Definitions and Outcome Measures	The primary outcomes for cohort 1 were progression-free survival (PFS) and duration of response (DOR). To minimize immortal time bias in the primary comparative analysis, time zero was defined as the last dose of ICI in the relevant course: the last dose of the rechallenge course for rechallenged patients and the last dose of the initial ICI course for non-rechallenged patients. PFS was defined as the time from this index date to progression or death, whichever came first. DOR was defined as the time from the first recorded response to the first ICI based on positron emission tomography–computed tomography (PET-CT) until progression. Secondary outcomes included the overall survival (OS) defined from the last dose of the relevant ICI course; the last dose of the rechallenge course for rechallenged patients and the last dose of the initial ICI course for non-rechallenged patients; to death from any cause, and the incidence and severity of irAEs after ICI rechallenge, graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Response was assessed from clinical and PET-CT findings using the Lugano classification. For exploratory analysis 1, time zero was the date of ICI discontinuation due to the index irAE, and time to progression was summarized descriptively because of the small sample size. For exploratory analysis 2, PFS was defined from the first dose of ICI rechallenge to progression or death. Event-free survival (EFS) was defined as the time from the first dose of ICI rechallenge to the first occurrence of disease progression, treatment discontinuation because of an AE, initiation of another systemic treatment for a reason other than an AE, or death. DOR was defined as the time from the first documented response after ICI rechallenge to progression or death. Patients still receiving ICI at the time of data cutoff were excluded from time-to-event analyses. Adverse events were classified by grade 1–5 and by organ system. Response categories included complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD).
Statistical Analyses	Baseline characteristics were summarized using medians and interquartile ranges (IQRs) for continuous variables and frequencies with percentages for categorical variables. Differences between groups were assessed using the Wilcoxon rank-sum test for continuous variables and the chi-square or Fisher's exact test, as appropriate, for categorical variables. OS, PFS, and DOR were estimated using the Kaplan–Meier method and compared between groups using the log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox proportional hazards models.

	Because patients selected for ICI rechallenge likely differed from those who were not rechallenged, propensity score matching (PSM) was performed for the primary analysis using 1:3 nearest-neighbor matching with replacement and a caliper of 0.2 on the logit of the propensity score. Prior autologous stem cell transplant before initial ICI exposure and the Hasenclever International Prognostic Score (IPS) were included in the propensity model. Patients without a response to ICI, missing response assessment, and with insufficient follow-up data to measure response end, were excluded from DOR analysis. Balance across matched cohorts was evaluated using standardized mean differences. All statistical tests were two-sided, and a p-value of less than 0.05 was considered statistically significant. Analyses were performed using R software (version 4.3.2).
Ethics Approval	The study was approved by the Mayo Clinic Institutional Review Board as a retrospective medical records study (25-008536). All research activities were conducted following the principles of the Declaration of Helsinki and institutional guidelines for human subject research.

Table S2. Characteristics of the propensity-score matched cohorts using autologous stem cell transplant status and the Hasenclever International Prognostic Score

	Rechallenge N=9 n (%)	No Rechallenge N=25 n (%)	*p*-Value
Age (Years)	39 (27–71)	39 (25–62)	0.70
Female	5 (56)	11 (44)	0.55
Ethnicity			
White	9 (100)	22 (88)	0.76
ECOG PS			0.26
0-1	8 (89)	24 (96)	
2-3	1 (11)	1 (4)	
Stage			0.57
II	2 (22)	10 (40)	
III	2 (22)	3 (12)	
IV	5 (56)	12 (48)	
IPS	3 (2–5)	3 (1–3)	0.51
Initial ICI in the R/R setting	6 (67)	18 (72)	0.76
Number of ICI cycles	6 (3–15)	6 (4–26)	0.50
Follow-up Periods (month, IQR)	33.9 (14.3-79.4)	48.0 (28.3-75.0)	0.51
Prior lines of Therapy before ICI (median, IQR)	1 (0-3)	1 (0-3)	0.55
BV prior to ICI	4 (44)	11 (44)	0.98
Auto-SCT prior to ICI	3 (33)	9 (36)	0.89
Auto-SCT after ICI	2 (22)	5 (20)	0.89

Abbreviations: Auto-SCT, autologous stem cell transplant; BV, brentuximab vedotin; ECOG PS, performance status; ICI, immune checkpoint inhibitor; IPS, Hasenclever International Prognostic Score; R/R, relapsed or refractory

Table S3. Clinical details of patients with relapsed/refractory cHL within cohort 1 who received ICI as second-line or later and discontinued treatment because of irAEs (exploratory analysis 1)

Patient No./Age/Sex	Rechallenge after irAE (Y or N)	Treatment line (n)	ICI agent	*Index irAE type/grade*	*Time to discontinuation (month)*	*Time from discontinuation to rechallenge (month)*	*Initial ICI response*	*Disease status before rechallenge*	*Rechallenge with same ICI (Y or N)*	*Recurrent irAE/type/grade*	*Rechallenge ICI response*
1/26/M	Y	4	P	Ocular myositis/1	6.3	8.5	CR	SD	Y	N	CR
2/39/M	Y	3	N	IRR/1	0.70	24.8	CR	SD	Y	N	PD
3/39/F	Y	4	P	Pneumonitis/2	13.8	15.4	CR	SD	Y	N	CR
4/54/M	Y	3	N	Hepatitis/2	0.78	3.0	SD	SD	Y	N	PR
5/77/F	Y	2	P	Pancreatitis/2	1.5	46.3	CR	SD	Y	Y/Pneumonitis/4	CR
6/39/M	Y	3	N	Colitis/2	10.5	15.6	CR	SD	Y	N	PD
7/21/F	Y	5	P	Aseptic meningitis/1	0.60	1.2	CR	SD	Y	N	CR
8/27/F	Y	7	N	Pleuritis/2	18.7	10.0	CR	SD	Y	Y/Pneumonitis/4	SD
9/66/M	Y	3	P	Nephritis/3	0.70	6.0	SD	SD	Y	N	CR
10/73/F	N	2	P	AIHA/3	7.6	-	CR		-	-	-
11/66/M	N	3	N	Neuritis/3	0.70	-	CR		-	-	-
12/23/M	N	7	P	Pneumonitis/2	65.9	-	SD		-	-	-
13/94/F	N	2	P	Fatigue/1	10.0	-	PR		-	-	-

Abbreviations: AIHA, autoimmune hemolytic anemia; CR, complete response; ICI, immune checkpoint inhibitor; IRR, infusion-related reaction; irAE, immune-related adverse event; N, nivolumab; P, pembrolizumab; PD, progressive disease; PR, partial response; SD, stable disease.

Table S4. Clinical details of patients in exploratory analysis 2

Patient No./Age/Sex	Initial ICI Treatment line (n)	Initial ICI	*Reason for ICI discontinuation*	*Initial ICI response*	*Treatment between the 1st and 2nd ICI*	*Disease status before rechallenge*	*Rechallenge with same ICI (Y or N)*	*Rechallenge ICI response*
1/49/M	2	P	Progression	PD	None	PD	N	PD
2/67/M	2	P	Progression	PD	None	PD	N	CR
3/59/M	5	N	Progression	PD	Allo SCT+BV, EV, Len	PD	N	CR
4/23/M	13	P	Progression	PD	GemOX	PD	N	PD
5/68/F	2	N	Progression	PD	None	PD	N	PR
6/29/M	2	N	Progression	PD	None	PD	N	PR
7/38/M	11	P	Progression	PD	EV	SD	N	PD
8/77/F	2	N	Progression	PD	RT	PD	N	CR
9/25/F	2	P	Treatment completion	PR	Auto SCT, RT	PD	Y	PD
10/26/F	2	N	Treatment completion	PR	Auto SCT	PD	Y	CR
11/62/M	3	N	Treatment completion	CR	None	PD	N	CR
12/56/M	3	N	Treatment completion	CR	None	PD	Y	CR
13/33/F	5	N	Treatment interruption	CR	BV	PD	Y	CR
14/31/F	7	N	Treatment completion	CR	None	PD	Y	CR
15/40/M	5	N	Treatment completion	CR	4 clinical trials, RT	PD	Y	CR

Abbreviations: Allo SCT, allogeneic stem cell transplant; Auto SCT; autologous stem cell transplant; AIHA, autoimmune hemolytic anemia; BV, brentuximab vedotin; CR, complete response; EV, everolimus; GemOx, gemcitabine and oxaliplatin; ICI, immune checkpoint inhibitor; IRR, infusion-related reaction; irAE, immune-related adverse event; L, lenalidomide; N, nivolumab; P, pembrolizumab; PD, progressive disease; PR, partial response; RT, radiation therapy; SD, stable disease.

Figure S1. STROBE diagram of the included patients

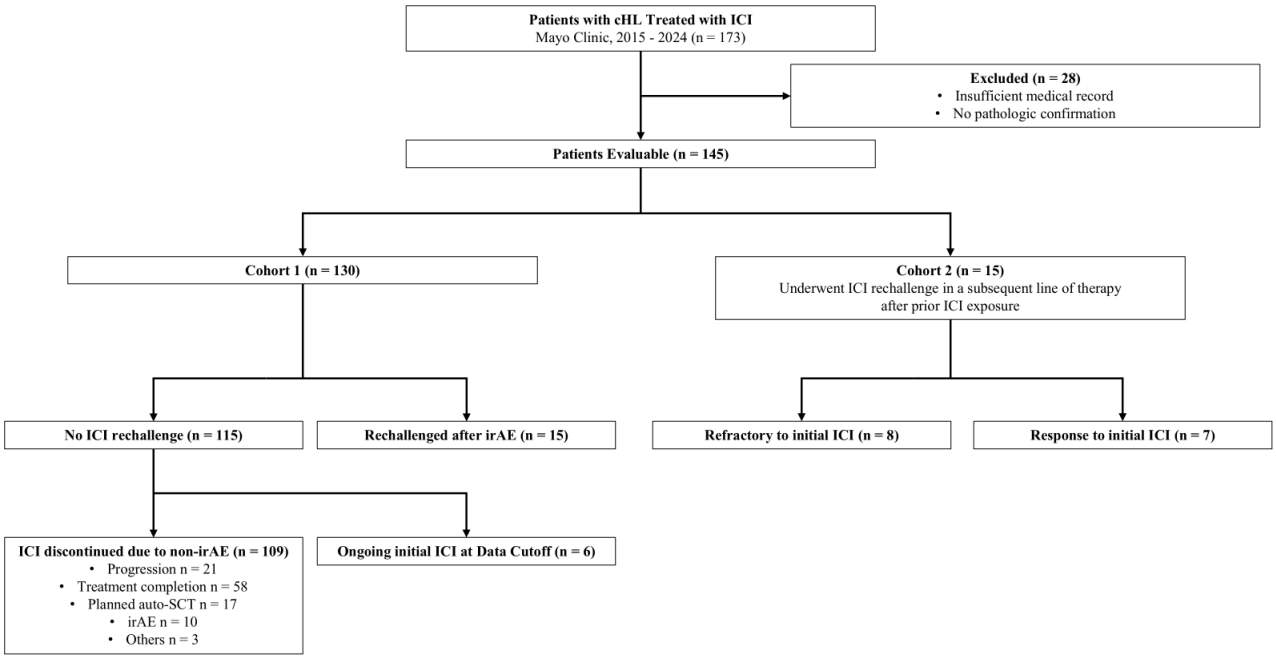


Figure S2. Propensity score distributions: autologous stem cell transplant status and the Hasenclever International Prognostic Score were used for the propensity score

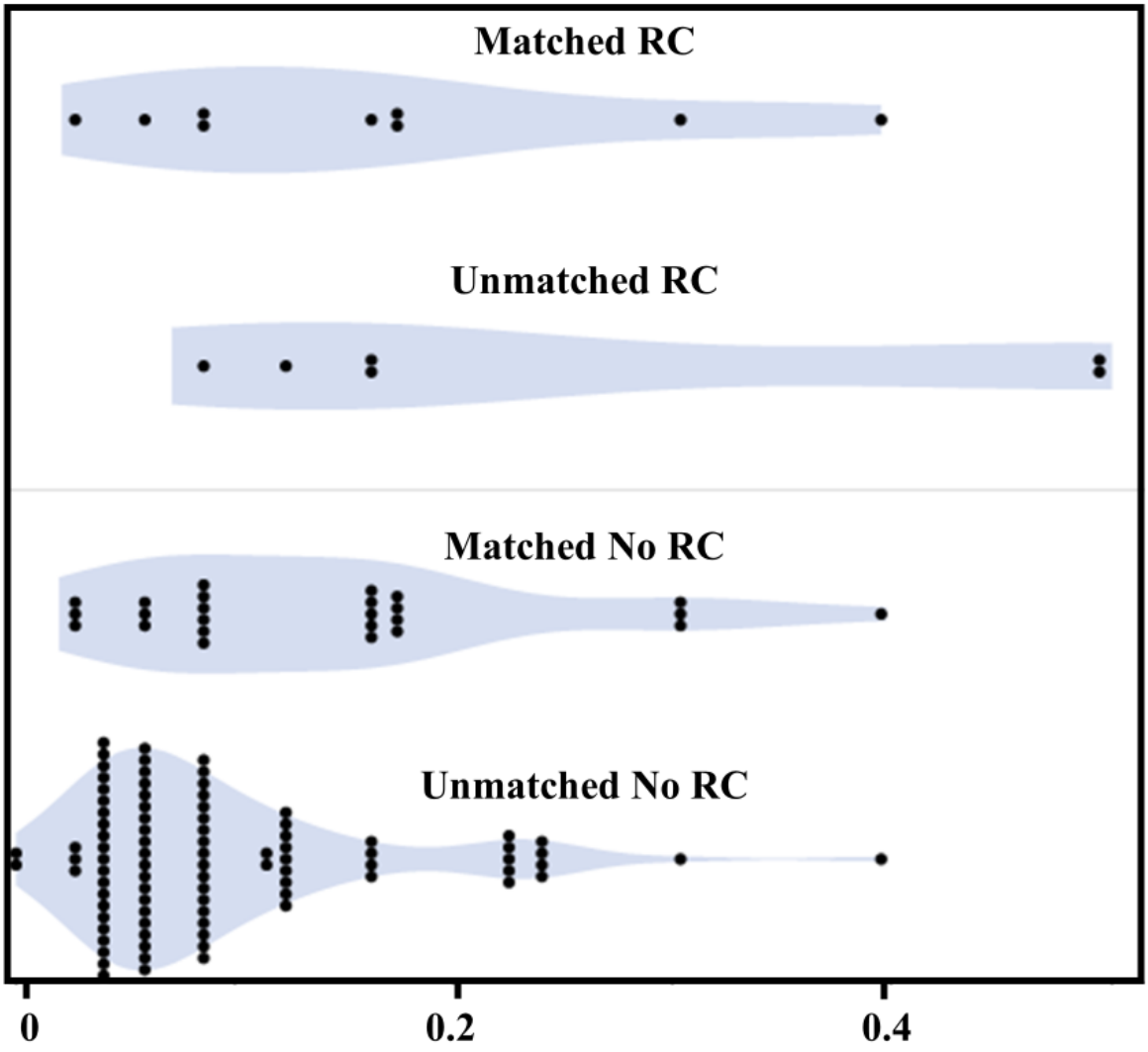
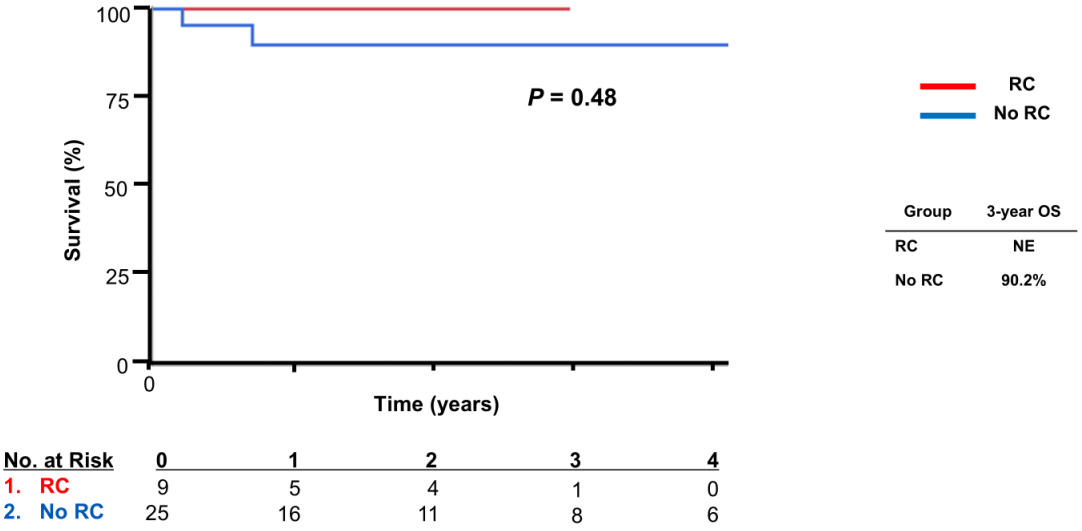


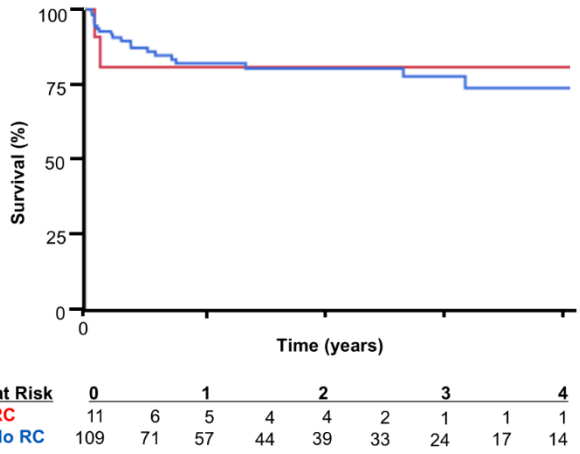
Figure S3. Overall survival in the propensity-score matched cohorts measured from the last ICI exposure



No. at Risk	0	1	2	3	4
1. RC	9	5	4	1	0
2. No RC	25	16	11	8	6

Figure S4. Unadjusted survival outcomes of patients who had immune checkpoint inhibitor rechallenge after adverse events; (A) Progression-free survival (B) Duration of response

(A)

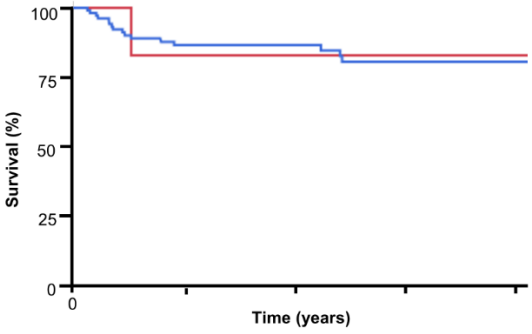


No. at Risk	0	1	2	3	4
1. RC	11	6	5	4	4	2	1	1	1
2. No RC	109	71	57	44	39	33	24	17	14

Group	Hazard ratio (95% CI)	P-value
No RC	Reference	
RC	1.1 (0.27-4.9)	0.85

Group	3-year PFS
No RC	77.6%
RC	80.8%

(B)



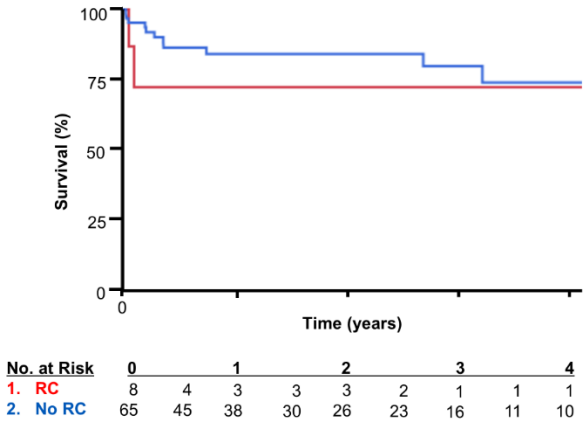
No. at Risk	0	1	2	3	4
1. RC	8	6	4	2	2	2	2	1	1
2. No RC	107	85	70	57	49	39	26	22	19

Group	Median DOR (months), IQR	Hazard ratio (95% CI)	P-value
No RC	103.9 (103.9-NR)	Reference	
RC	NR (6.2-NR)	0.94 (0.12-7.1)	0.95

Group	3-year DOR
No RC	80.7%
RC	83.3%

Figure S5. Progression-free survival subgroup analyses; (A) Relapsed or refractory disease (B) Non-relapsed or refractory disease (C) Patients who discontinued ICI because of an irAE

(A)



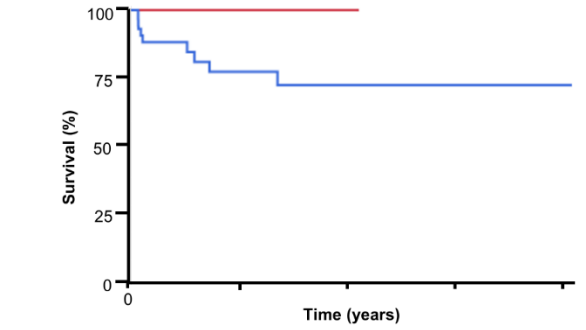
No. at Risk	0	1	2	3	4
1. RC	8 4 3	3	3 2	1	1 1
2. No RC	65 45 38	30	26 23	16	11 10

RC
No RC

Group	Hazard ratio (95% CI)	P-value
No RC	Reference	
RC	1.8 (0.41-8.3)	0.43

Group	3-year PFS
No RC	80.3%
RC	72.9%

(B)

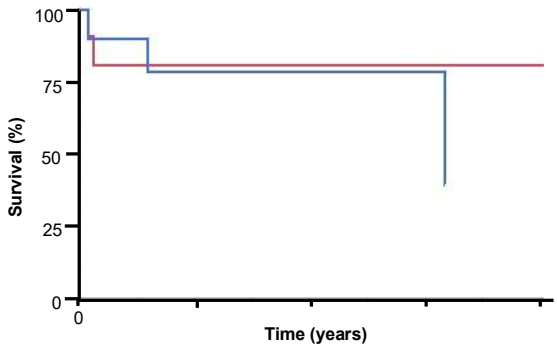


No. at Risk	0	1	2	3	4
1. RC	3 2 2	1	1 0	0	0 0
2. No RC	44 25 18	13	12 10	7	5 3

RC
No RC

Group	3-year PFS
No RC	NE
RC	72.9%

(C)



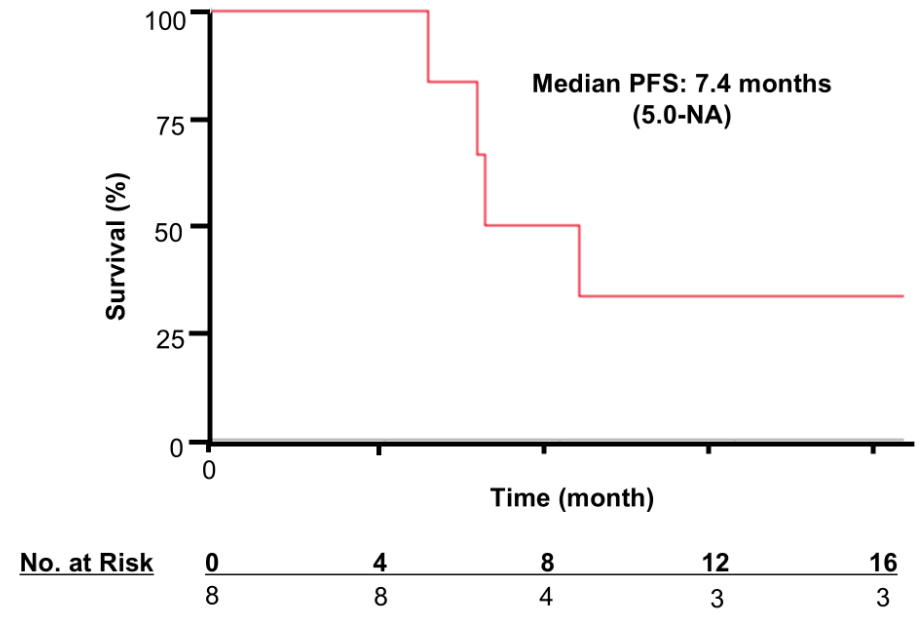
No. at Risk	0 1 2 3 4								
1. RC	11	7	6	5	5	3	2	2	1
2. No RC	10	9	7	7	5	5	4	0	0

RC
No RC

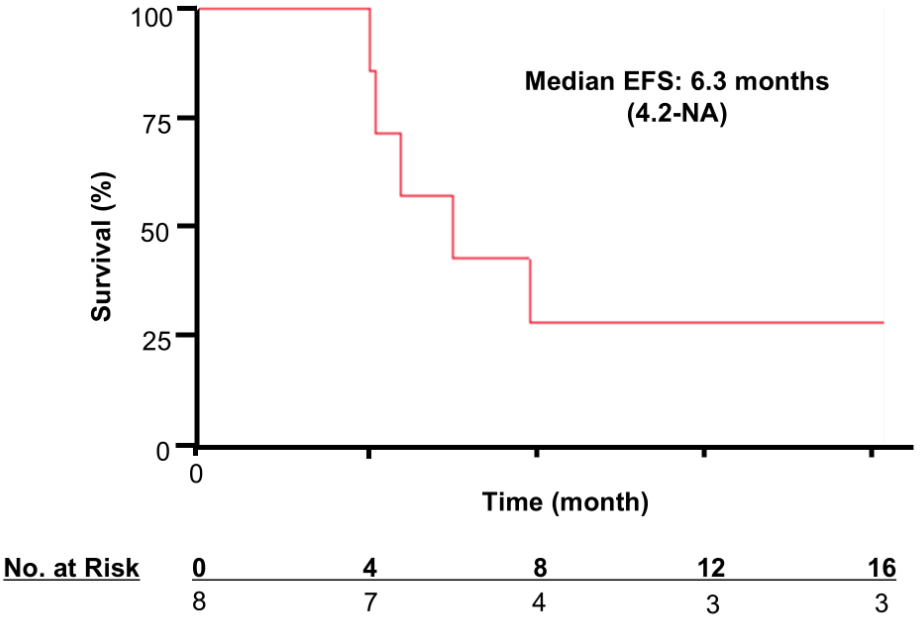
Group	Hazard ratio (95% CI)	P-value
No RC	Reference	
RC	0.79 (0.13-4.8)	0.80

Figure S6. Survival outcomes after subsequent-line ICI rechallenge in patients with disease refractory to initial ICI: (A) progression-free survival and (B) event-free survival

(A)



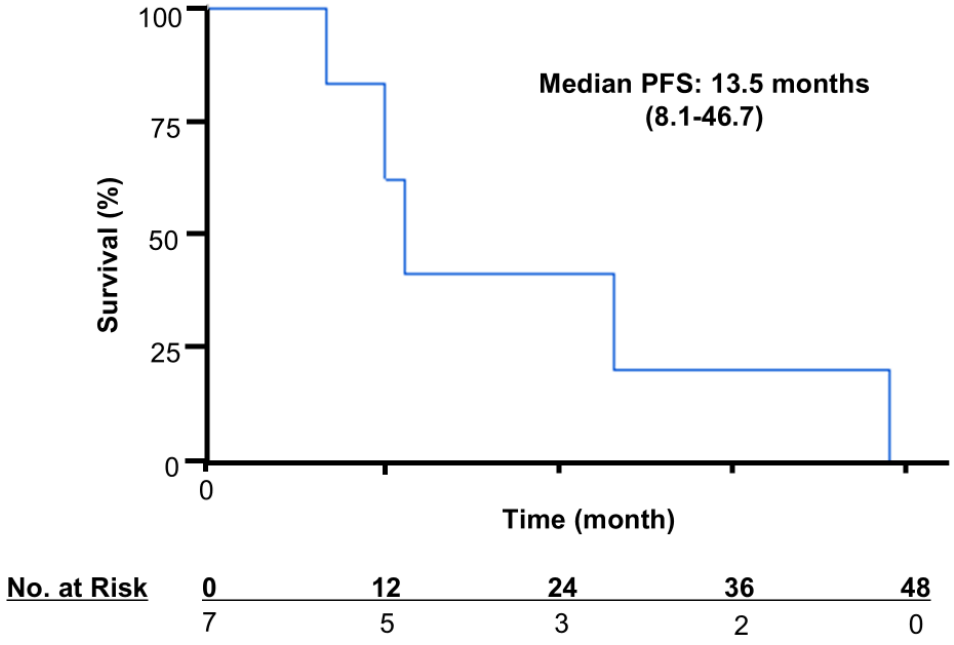
(B)



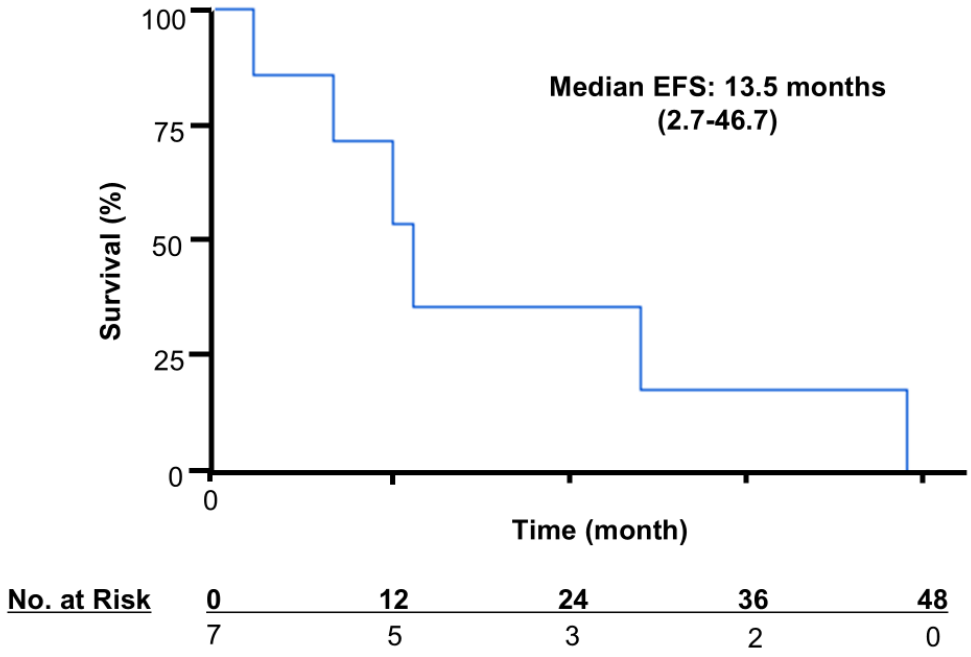
Abbreviations: EFS, event-free survival; NA, not applicable; PFS, progression-free survival

Figure S7. Survival outcomes after ICI rechallenge at relapse in patients who previously achieved complete or partial response to initial ICI: (A) progression-free survival and (B) event-free survival

(A)



(B)



Abbreviations: EFS, event-free survival; NA, not applicable; PFS, progression-free survival