Prognostic Factors in Patients with Advanced Non-Small Cell Lung Cancer after Long-Term Anti-PD-1 Therapy (HOT1902)

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Abstract:

Objectives: Limited information is available on the appropriate treatment duration of immune checkpoint inhibitors (ICIs). We aimed to identify candidates who would benefit from ICI discontinuation after one year of treatment for metastatic non-small cell lung cancer (NSCLC).

Materials and Methods: This retrospective multi-institutional observational study examined medical records of all consecutive patients with advanced or recurrent NSCLC, who started ICI monotherapy at 15 institutions in Japan between December 2015 and December 2017. Patients who received initial ICI therapy for >1 year without progressive disease were defined as the long-term treatment (LT) group; others were defined as the non-long-term treatment (NLT) group. Primary outcomes included the prognostic factors in the LT group, whereas secondary outcomes included efficacy of ICI rechallenge, safety, and survival outcomes in the overall population.

Results: In total, 676 patients were enrolled, and 114 (16.9%) were assigned to the LT group. The median time interval from the start of initial ICI administration to data cutoff was 34.3 months (range, 24.1 to 47.8); thus, all surviving patients were followed-up for at least 2 years from the start of initial ICI. Median progression-free survival (PFS) was longer in the LT than in the NLT group (33.6 months vs. 2.7 months; $p<.001$). On multivariate analysis, significantly better PFS was associated with smoking (hazard ratio [HR]=0.36, $p=.04$), and complete

response (CR; HR=uncomputable, $p<.001$) in the LT group. Thirty-seven patients (5.5%) received ICI rechallenge, including 10 in the LT group. Among patients receiving rechallenge treatment, the median PFS was 2.2 months, with no difference between the LT and NLT groups.

Conclusions: In the LT group, smoking and achieving CR were significantly associated with better PFS. Since rechallenge treatment was not effective, careful consideration is required for discontinuing ICI. However, these prognostic factors are helpful in considering candidates for ICI discontinuation.

Trial Registration

UMIN ID, UMIN000041403

Keywords: immune checkpoint inhibitor, pembrolizumab, nivolumab, non-small-cell lung cancer, ICI rechallenge

Classification

Retrospective cohort study

Abbreviations

AE: adverse events

AEC: baseline absolute eosinophil count

ALC: baseline absolute lymphocyte count

ANC: absolute neutrophil count

CIs: 95% confidence intervals

CR: complete response

ECOG PS: Eastern Cooperative Oncology Group performance status

HRs: hazard ratios

ICIs: immune checkpoint inhibitors

irAEs: immune-related AEs

LT: long-term treatment

NLT: non-long-term treatment

NSCLC: non-small cell lung cancer

OS: overall survival

OSR: overall survival of rechallenge treatment

PD-1: programmed cell death protein-1

PD-L1: programmed death-ligand-1

PD: progressive disease

PFS: progression-free survival

PFSR: progression-free survival of rechallenge treatment

PR: partial response

RECIST 1.1: Response Evaluation Criteria in Solid Tumors version 1.1

1. Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of all lung cancers, with the majority of cases being unresectable and metastatic at the time of initial diagnosis [2]. Programmed cell death protein-1 (PD-1)/programmed death-ligand-1 (PD-L1) inhibitors have shown efficacy in the treatment of advanced NSCLC and have become a standard of care [3-7].

Generally, anticancer drug treatment continues until the patients experience disease progression or unacceptable toxicity. However, immune checkpoint inhibitors (ICIs) are known to achieve long-lasting responses after therapy discontinuation due to adverse events (AEs) or reaching a specified number of treatment courses [8,9]. As some patients experience new immune-related AEs (irAEs) even after long-term ICI administration [10], or the cost of these drugs is elevated, identifying the appropriate ICI treatment period is crucial. In legislation trials, pembrolizumab was developed for use for up to two years [5]; thereafter, it may be discontinued. Progression-free survival (PFS) curves of nivolumab treatment showed a so-called “tail plateau” after a sharp decline since the initiation of ICI administration until approximately one year [3, 4, 9]. Additionally, a long-term follow-up study of phase I trials on ICIs for multiple cancer types, in which NSCLC accounted for only 9.5% (25 patients) of the total cohort, showed that even in responders, those discontinuing treatment within 12 months

had a higher recurrence risk. Moreover, analysis of patients who were treated with ICIs for a given period or those who discontinued treatment due to AEs, showed that patients with complete response (CR) had a lower recurrence rate after treatment discontinuation [11]. Therefore, some patients treated with ICIs for >1 year or with good overall response may be able to discontinue treatment before two years. However, these studies are post-hoc analyses using data from prospective clinical trials, and no study has investigated this topic using multi-institutional real-world data.

On the contrary, if rechallenge treatment, i.e., re-administration of ICIs (including anti-PD-L1 inhibitor after anti-PD-1 inhibitor or vice versa), is effective, discontinuing ICI treatment before experiencing disease progression or AEs will be advantageous for the patients. Some studies have investigated the efficacy and prognostic factors of rechallenge treatment [12-16]. However, the efficacy of ICI rechallenge treatment in patients who received initial ICI treatment and achieved disease control for >1 year has not been studied. It is worth investigating whether ICI rechallenge is beneficial in certain patients, especially those initially treated with ICI for >1 year.

The aims of this retrospective study were to 1) describe the clinicopathological characteristics of patients undergoing long-term initial ICI treatment; 2) investigate prognostic

factors in patients undergoing long-term initial ICI treatment; and 3) identify candidates who would benefit from ICI rechallenge treatment.

2. Materials and methods

2.1. Study design and participants

HOT1902 was a retrospective multicenter study of NSCLC patients who started anti-PD-1 inhibitor monotherapy between December 2015 and December 2017. We reviewed the medical records of all consecutive patients with advanced or recurrent NSCLC treated with nivolumab or pembrolizumab at 15 institutions belonging to the Hokkaido Lung Cancer Clinical Study Group Trial (HOT) in Japan. We did not set any exclusion criteria to avoid selection bias; all patient data were included in the analysis unless essential clinical data were missing. The data cut-off date was December 31, 2019. This study was registered at UMIN-CTR (UMIN000041403) and approved by the institutional review boards at all institutions; the need for informed consent was waived because anonymized data were analyzed in this study.

We defined patients who underwent initial ICI treatment for >1 year without progressive disease (PD) as the long-term treatment (LT) group, and others as the non-long-term treatment (NLT) group. We defined rechallenge as re-administration of ICIs for patients who were previously treated with ICIs, had discontinued this treatment, and had confirmed PD thereafter.

Owing to the timing of drug approval in Japan, only PD-1 inhibitors (nivolumab or pembrolizumab) were used as initial ICI treatment. In addition to PD-1 inhibitors, the PD-L1 inhibitor atezolizumab was used as ICI rechallenge treatment. Data on the following characteristics were collected: age, sex, smoking status, pack-years, histology, cancer stage, tumor burden, presence of driver mutation, PD-L1 status, history of radiation therapy within six weeks before ICI treatment initiation, steroid administration at ICI treatment initiation, baseline absolute neutrophil count (ANC), baseline absolute lymphocyte count (ALC), baseline absolute eosinophil count (AEC), Eastern Cooperative Oncology Group performance status (ECOG PS) at the start of initial ICI treatment, number of treatment lines before initial ICI administration, clinical response to ICI treatment, irAE type and grade with which ICI treatment was discontinued, and the presence of ICI rechallenge treatment. Tumor response was measured using the Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1). Owing to the retrospective design, CR and partial response (PR) did not need confirmation. Assessments were performed at each participating institution. Tumor burden was defined as the sum of the longest diameters for a maximum of five target lesions, and up to two lesions per organ. We only collected information regarding irAEs that caused treatment discontinuation.

A previous report suggested that a baseline signature of a low ANC, high ALC, and high AEC is associated with a better outcome of ICI treatment [17]. Following this study, the cut-off

values for blood cell counts were set as 7500/μL for ANC, 1000/μL for ALC, and 150/μL for AEC. We defined patients with all three favorable factors as group A, those who had two factors as group B, and one or no factor as group C.

2.2. Statistical analysis

Qualitative variables were reported as frequency (percentage). Quantitative variables (age, pack-years, and tumor burden) were reported as medians with ranges; χ^2 and Fisher's exact tests for independence were used to compare qualitative variables. Age, pack-years, and tumor burden were compared using a Wilcoxon rank-sum test. PFS was defined as the interval between initial ICI administration and disease progression or death. Overall survival (OS) was defined as the interval between initial ICI administration and death from any cause. PFS of rechallenge treatment (PFSR) was defined as the interval between the beginning of the ICI rechallenge treatment and disease progression or death. The OS of rechallenge treatment (OSR) was calculated from the beginning of the ICI rechallenge treatment to death from any cause. The ICI administration period was calculated from the date of initial ICI administration to the date of last administration of initial ICI therapy. Patients without documented clinical or radiographic disease progression or those still alive were censored on the date of the last follow-up. PFS, OS, and PFSR were evaluated using the Kaplan–Meier method and compared using a two-sided log-rank test. Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated

using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and medical point of view were selected for inclusion in multivariate analysis. All *p*-values were two-sided and the threshold for statistical significance was set at $p<.05$. All statistical analyses were performed using JMP Pro 14 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

In total, 676 NSCLC patients who were administered immunotherapy with PD-1 inhibitors were enrolled in the study; 519 (76.8%) received nivolumab and 157 (23.2%) received pembrolizumab as initial ICI treatment. Patient characteristics are listed in Table 1. PD-L1 expression was not investigated in approximately half of the patients. Overall, 75 patients discontinued ICI after only one course of treatment. Among them, 12 cases had a PS of 3 or 4; although these patients are usually not likely to be eligible for ICI administration, they merely comprised less than 1.8% of the overall cohort. The LT group had 114 patients, comprising 16.9% of all patients enrolled in the study. The median age in the LT group was 67 years (range: 43–84). Most patients in the LT group were men (n=95, 83.3%), had a smoking

history (n=107, 93.9%), were heavy (>30 pack-years) smokers (n=88, 77.2%), had a performance status (PS) of 0 or 1 (n=108, 94.7%), and had no driver mutations (n=111, 97.4%).

3.2. Clinical outcomes

The median interval from the beginning of initial ICI administration to data cut-off was 34.3 months (range, 24.1–47.8); thus, all surviving patients were followed up for at least two years from initial ICI administration. The Kaplan–Meier curves for PFS and OS in all patients are shown in Figure S1. The median PFS was 3.6 (95% CI, 3.1–4.1) months and the median OS 12.9 (95% CI, 11.6–14.3) months. Regarding tumor response, the objective response rate was 26.3%; 21 (3.1%) patients achieved CR, and 157 (23.2%) achieved PR. We did not collect information regarding pseudoprogression; the rate and number of patients with pseudoprogression were therefore unknown in this study. A significantly better response was found in the LT group than in the NLT group (81.6% vs. 15.1%, p<.0001) (Table S1 and Figure S2). To identify the variables affecting the PFS and OS of the overall population, univariate and multivariate analyses were performed. On multivariate analysis, male sex, smoker, less tumor burden (<45 mm), ECOG PS (0 or 1), tumor response (CR), and irAE presence were independent favorable prognostic factors for PFS (Table S2). On multivariate analysis, stage (stage III or recurrence), lower tumor burden (<45 mm), number of prior treatments (0 or 1), ECOG PS (0 or 1), tumor response (CR), and the presence of irAEs were independent favorable

prognostic factors for OS (Table S3). The Kaplan–Meier curves for PFS and OS by subgroup are presented in Supplementary Figures S3 and S4.

The median PFS was longer in the LT group (33.6 months; 95% CI, 27.2 –not reached) than in the NLT group (2.7 months; 95% CI, 2.3–3; $p<.001$; Figure 1A), and the median OS was longer in the LT group (median, not reached; 95% CI, 41.5 months–not reached) than in the NLT group (9.4 months; 95% CI, 8.3–11.0; $p<.001$; Figure 1B).

We then investigated the prognostic factors in patients in the LT group (Table 2). Univariate Cox proportional hazard regression analysis revealed that male sex, smoker, PS (≥2) at ICI treatment initiation, and tumor response were related to favorable PFS. We performed multivariate Cox proportional hazard regression analysis including the smoking status, tumor burden, PS, tumor response, and radiation therapy in terms of PFS. Smoking and tumor response (CR) were significantly associated with better PFS (Table 2). Notably, all patients with CR (n=14) and 5 of 6 patients with PS (≥2) at ICI treatment initiation did not show disease progression (Supplementary Figure S5). Only one of six patients with poor PS at ICI administration died after ICI treatment was discontinued due to dementia and was transferred to the local hospital; the cause of death was unknown. One patient with PS 2 at ICI treatment initiation achieved CR in the LT group. Regarding OS, univariate Cox proportional hazard regression analysis revealed that the number of prior treatments (0 or 1), PD-L1

expression (PD-L1: 1-49%), tumor response (CR), and irAE presence were related to favorable OS (Table S4). As only 22 patients (19.2%) had OS events in the LT group, the number of multivariate analysis factors in terms of OS was limited. Significantly worse OS was associated with the number of prior treatments (≥2) (HR=2.43; 95%CI, 1.02–6.21, *p*=.0449; Table S4). The Kaplan–Meier curves for PFS and OS by each subgroup are presented in Figure S5 and Figure S6.

To investigate the relationship between treatment duration and prognosis in the LT group, both the 6-month/1-year PFS rate calculated at 1, 1.5, and 2 years after ICI treatment initiation were analyzed (Figure S7). The number of patients who were able to undergo ICI treatment without PD >1.5 years was 76 (of 676, 11.2%) and >2 years was 59 (of 676, 8.7%). The median durations of follow-up from 1-year/1.5-year/2-year ICI treatment to the data cut-off were 20.0 months (range, 12.1–35.6), 13.5 months (range, 6.1–28.7), and 7.6 months (range, 0.8–22.7), respectively. In each subgroup, the 6-month PFS rates were 79.8, 89.5, and 80.2%, and the 1-year PFS rates were 69.9, 72.2, and 76.5%, respectively. Thus, even in the LT group, the PFS rate continued to decline regardless of ICI treatment duration.

Finally, the efficacy of the rechallenge treatment was evaluated. Clinicopathological characteristics of patients receiving ICI rechallenge treatment are listed in Table 3. In total, 37 patients (5.5% of all patients) were administered two lines of anti-PD-1/PD-L1 agents; among

them, 10 patients (27%) were included in the LT group. The median duration of follow-up from rechallenge treatment initiation to data cut-off was 14.0 months (range, 0.9–34.2). Among the overall rechallenge patients, the median PFSR was 2.2 months (95% CI, 1.5–4.3). In the LT group, the median PFSR was 2.9 months (95% CI, 0.7–8.3), which was practically the same as that in the NLT group, at 2.0 months (95% CI, 1.4–6.6; Figure 2). The median OSR was 10.7 months (95% CI, 4.4–16.0, Fig. S8). On univariate analysis of the prognostic factors for PFSR, the median PFSR was significantly longer in patients who achieved PR or CR on the initial ICI (3.8 months, 95% CI, 1.5–not reached vs. 1.9 months, 95% CI, 0.8–3.7, *p*=.0381) (Table S5), had reasons of discontinuation other than PD (6.6 months, 95% CI, 1.5–not reached vs. 1.8 months, 95% CI, 1.1–2.8, *p*=.0122), or achieved PFS ≥3 months after the initial ICI treatment discontinuation (6.6 months, 95% CI, 1.5–not reached vs. 1.8 months, 95% CI, 1.4–2.8, *p*=.0122) than those who did not. Among the 37 patients treated with ICI rechallenge, 21 of 37 received the same anti-PD-1 drug as for prior ICI therapy; 16 patients switched to atezolizumab, a PD-L1 inhibitor. There was no significant difference between the median PFSR of patients treated with PD-1 and PD-L1 (2.3 months, 95% CI, 1.4–10.3 vs. 2.1 months, 95% CI, 1.4–4.3, p=.3184).

3.4. Safety

In the LT group, 24 of 114 (21.1%) patients discontinued ICI treatment due to irAEs. Among them, 33.3% (8 patients) had irAEs ≥grade 3. The rate of patients who discontinued ICI treatment because of irAEs in the LT group was similar to that of the overall cohort (20.4%, 138 patients). Although more than half of the irAEs occurred within 24 months of ICI administration, new-onset irAEs occurred even >3 years after ICI treatment initiation, leading to treatment termination (Figure 3). The most frequently reported irAE was pneumonitis (n=12; 10.5% of LT group; Table S6).

4. Discussion

To the best of our knowledge, this is the first multi-institutional study to investigate the clinical course in patients receiving ICI treatment for >1 year in the real world. Our study included data from a relatively large number of consecutive patients, of whom the LT group comprised 16.9%. Overall, the efficacy and survival data of our patients were almost identical to those of previous reports that assessed ICI monotherapy in advanced NSCLC [17-28]. Therefore, the patient population in this study was considered suitable for further analysis. In 2019, Galli et al. studied the clinical course of 147 patients with NSCLC treated with ICIs (anti-PD-1/PD-L1 antibody and/or anti-CTLA4 antibody) in their institution (Instituto Nazionale de Tumori, Milan) [29]. They defined patients who obtained a CR/PR/SD as best response and

maintained it for at least 12 months, as the LTB (long-term benefit) group; other non-PD patients were defined as the STB (short-term benefit) group, and those with PD were defined as P (progressors). On comparing LTB and STB+P in a multivariate analysis, they concluded that best responses of CR/PR were associated with LTB. This conclusion was similar to ours; however, their study included no data regarding prognostic factors in the LTB group, or any data pertaining to patients who received ICI rechallenge. Our study investigated these issues further, in more than 4-fold the number of patients in a multi-center setting.

In our study, 21.1% of the patients in the LT group discontinued ICI treatment due to irAEs; this was equivalent to the rate of patients in the overall population. However, this rate was significantly higher than that in a previous study [10] because of several reasons. First, our study used real world data and patients were not selected. Second, as per the advice of the physician in charge, the patients discontinued ICI treatment regardless of irAE grade. Serious (grade ≥3) irAEs were a reason for discontinuation in only 8 of 24 (33.3%) patients, who experienced irAE and discontinued ICI treatment in the LT group. However, serious and life-threatening irAEs such as grade 4 encephalitis were newly experienced in the LT group. Thus, our study showed that long-term ICI administration did not guarantee the safety of long-term administration in the real world.

The median PFS in the LT group from initial ICI treatment was 33.6 months; this was similar to that of patients in the continuous group of Checkmate 153 [30]. Although this figure was considerably better than that of the overall population, even in the LT group, 22 of 114 (19.1%) patients died during the follow-up period. This implies that patients who relapsed after long-term ICI administration eventually died of lung cancer. Therefore, maintaining a longer PFS while considering the optimal ICI treatment period is important.

Interestingly, in the LT group, the PFS rates at six months (calculated from 1, 1.5, and 2 years after ICI treatment initiation) were approximately 80%. This suggests that a certain proportion of patients will relapse even if the treatment period is extended from one to two years. In the long-term analysis of KEYNOTE 010, the 1- and 2-year PFS rates were 72.5% and 57.7%, respectively, after completion of 2-year treatment [8]. Most patients experienced recurrence within one year of discontinuation; in cases with a high probability of recurrence, continuing ICI treatment even after two years may therefore be better [8]. In the Checkmate 153 trial, NSCLC patients who were treated with nivolumab for one year were assigned to either the treatment continuation group or the discontinuation group, and better survival was observed in the former [30]. Based on the above, treatment discontinuation must be considered carefully and individually even after long-term ICI administration.

Regarding rechallenge treatment, if such treatment is effective, then discontinuation of ICIs before disease progression or AEs may be useful, especially for patients in the LT group. However, the median PFSR in the LT group was only 2.9 months, which was significantly lower than the PFS with the initial ICI treatment. One of the prognostic factors in the rechallenge treatment group was discontinuation of the initial ICI treatment for reasons other than PD. However, even in the three patients who were able to undergo the initial ICI treatment for >1 year and discontinued for reasons other than PD, two presented PD within five months of rechallenge treatment initiation. Thus, terminating ICI treatment after long-term administration in anticipation of the effects of rechallenge treatment should be carefully considered in the context of clinical trials. The JCOG 1701, a prospective study comparing the treatment discontinuation and continuation groups in advanced or recurrent NSCLC patients who received PD-1 pathway inhibitors for >52 weeks, is ongoing [31].

In our study, multivariate analysis showed that smokers and patients achieving CR had a significantly better prognosis in terms of PFS in the LT group. In addition, though not statistically significant, the patients with a PS of 2 at initial ICI administration obtained good results. As previously reported, overall, patients with worse PS at ICI administration had the worst prognoses for PFS and OS in our study [26]. However, if a patient with PS 2 can continue ICI for >1 year without PD, this patient may obtain the same degree of treatment benefit (so-

called “super-responder”) from ICIs as those who experience CR. Additionally, a previous phase I study on multiple cancer types showed that patients who achieved CR and those able to receive ICI for >1 year had a good prognosis after ICI discontinuation [11]. Thus, in the LT group, patients with long-term response despite poor PS at the beginning of ICI treatment or those who achieved CR may be good candidates for ICI treatment discontinuation.

There are several limitations to the present study. First, this was a retrospective study; the data on PD-L1 expression and driver mutation in non-adenocarcinoma patients were insufficient. Second, the number of patients who received rechallenge treatment and some subgroups of the LT group were insufficient. Third, the shortest follow-up duration was two years; this observation period is insufficient for evaluating OS in the LT group. Another limitation was that PS and blood data at the start of the rechallenge treatment were not collected. Therefore, the analysis of the prognostic factors for rechallenge treatment could not be thoroughly performed. These limitations may have hindered the drawing of definite conclusions with considerable clinical guiding significance.

5. Conclusions

This is the first study to investigate the prognostic factors in patients receiving ICIs for >1 year in the real world. Our data provide insights into the efficacy and safety of long-term ICI

treatment in the real world. Until concrete evidence is established, the decision of ICI discontinuation should be carefully considered at the individual level, because some patients will present with PD even after long-term ICI administration and the efficacy of rechallenge treatment may be limited. However, the results of the analysis of prognostic factors for PFS in the LT group will be helpful in considering candidates for ICI treatment discontinuation.

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The other authors declare no conflicts of interest.

Data Availability Statement

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

Drs. Shotaro Ito and Hajime Asahina had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Shotaro Ito and Hajime Asahina.

Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Shotaro Ito and Hajime Asahina.

Critical revision of the manuscript for important intellectual content: All authors.

Statistical analysis: Shotaro Ito and Hajime Asahina.

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Tables

Table 1 Baseline and treatment characteristics of the study groups

Categorical data are presented as numbers (percentages) and have been compared using the X^2 and Fisher's exact tests. Continuous data are presented as medians (range) and have been compared using the Wilcoxon rank-sum test. The *p*-value was calculated by comparing subjects in the LT and NLT groups.

	No. (%)			
Characteristic	**All (n=676)**	**LT group (n=114)**	**NLT group (n=562)**	***p*-value[a]**
Age, years				
Median (range)	67 (34–85)	67 (43–84)	68 (34–85)	.2288
Sex				.003
Male	490 (72.5)	95 (83.3)	395 (70.3)	
Female	186 (27.5)	19 (16.7)	167 (29.7)	
Smoking status				.0014
Never smoked	102 (15.1)	7 (6.1)	95 (16.9)	
Current or former smoker	574 (84.9)	107 (93.9)	467 (83.1)	

Pack-years				
Median (range)	40 (0–330)	45 (0–156)	39 (0–330)	.0002
≥10	550 (81.4)	106 (93.0)	444 (79.0)	.001
≥30	426 (63.0)	88 (77.2)	338 (60.1)	.0004
≥50	225 (33.3)	48 (42.1)	177 (31.5)	.0307
Histology				.5098
Adenocarcinoma	415 (61.4)	67 (58.8)	348 (61.9)	
Squamous cell carcinoma	205 (30.3)	34 (29.8)	171 (30.4)	
Non-small cell lung carcinoma	26 (3.8)	5 (4.4)	21 (3.74)	
Large cell carcinoma	14 (2.1)	3 (2.6)	11 (1.96)	
Others	16 (2.4)	5 (4.4)	11 (1.96)	
Disease stage at diagnosis				.5824
III	153 (22.6)	29 (25.4)	124 (22.1)	
IV	397 (58.6)	62 (54.4)	335 (59.6)	
Recurrence	126 (18.6)	23 (20.2)	103 (18.3)	
Tumor burden (mm)				.1311
Median (range)	53 (0–330)	47 (0–214)	55 (0–330)	
Driver mutation				.3616

EGFR sensitizing mutation	53 (7.8)	2 (1.8)	51 (9.1)	
ALK translocation	5 (0.7)	0 (0)	5 (0.9)	
ROS1	5 (0.7)	1 (0.9)	4 (0.7)	
BRAF	3 (0.4)	0 (0)	3 (0.5)	
Others	8 (1.2)	0 (0)	8 (1.4)	
Not investigated	602 (89.1)	111 (97.4)	491 (87.4)	
Number of prior treatments				.0011
0	84 (12.4)	26 (22.8)	58 (10.3)	
1	283 (41.8)	48 (42.1)	235 (41.8)	
≥2	309 (45.7)	40 (35.1)	269 (47.9)	
Performance status				<.0001
0	118 (17.4)	29 (25.4)	89 (15.8)	
1	430 (63.6)	79 (69.3)	351 (62.5)	
2	100 (14.8)	6 (5.3)	94 (16.7)	
≥3	28 (4.1)	0 (0)	28 (5.0)	
PD-L1 status (22C3 IHC)				<.0001
<1%	40 (5.9)	3 (2.6)	37 (6.6)	
1-49%	67 (9.9)	15 (13.2)	52 (9.3)	

≥50%	146 (21.6)	43 (37.7)	103 (18.3)	
Unknown	423 (62.5)	53 (46.5)	370 (65.8)	
WBC fraction				.2535
Group A	168 (24.9)	34 (29.8)	134 (23.8)	
Group B	305 (45.1)	52 (45.6)	253 (45.0)	
Group C	203 (30.0)	28 (24.6)	175 (31.1)	
Radiation therapy				.8703
Irradiation	86 (12.7)	14 (12.3)	72 (12.8)	
No irradiation	590 (87.3)	100 (87.7)	490 (87.2)	
Steroid use at ICI treatment initiation				.0827
Yes	53 (7.8)	4 (3.5)	49 (8.7)	
No	623 (92.2)	110 (96.5)	513 (91.3)	
ICI type				<.0001
Nivolumab	519 (76.8)	69 (60.5)	450 (80.1)	
Pembrolizumab	157 (23.2)	45 (39.5)	112 (19.9)	

Abbreviations: CR, complete response; ICI, immune checkpoint inhibitor; LT group, patients receiving initial ICI for >1 year without progressive disease (PD); NE, not evaluable; NLT

group, patients other than LT group; No, number; PD, progressive disease; PD-L1, programmed death-ligand-1; PR, partial response; SD, stable disease; WBC, white blood cell.

[a] $p < .05$ was considered statistically significant.

Table 2 Univariate and multivariate analyses of PFS in the LT group

Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using the Cox proportional hazards regression model. Without considering the results of the univariate analysis, the factors considered important from the results of the previous report and the medical point of view were selected for inclusion in multivariate analysis.

		Univariable			**Multivariable**		
Parameter	**Category**	**HR**	**95% CI**	***p*-value**	**HR**	**95% CI**	***p*-value**
Age (years)	≥75 (vs. <75)	0.91	0.41–1.77	0.7894			
Sex	Female (vs. Male)	3.47	1.85–6.26	.0002			
Smoking Status	Smoker (vs. Never)	0.30	0.14–0.79	.0165	0.36	0.16–0.96	.0423
Pack-years	≥30 (vs. <30)	0.65	0.37–1.22	0.1718			
Histology	Ad (vs. others)	0.99	0.58–1.73	0.9812			
Stage at diagnosis	Stage IV (vs. others)	1.36	0.79–2.39	0.2622			
Tumor burden	<45 mm (vs. ≥45mm)	0.71	0.40–1.24	0.2307	0.77	0.43–1.36	.380
No. of prior therapy	≥2 (vs. 0 or 1)	1.39	0.80–2.38	0.2398			
Performance Status	≥2 (vs. 0 or 1)	0.21	0.01–0.98	0.0459	0.24	0.01–1.11	.0730

PD-L1 status	1–49% (vs. <1%)	0.24	.046–1.73	0.1375			
	≥50% (vs. <1%)	0.48	0.14–3.00	0.3684			
Response Category	CR (vs. others)	NA[a]	0.22–0.22	<.001	NA[a]	0.00-0.26	.0002
	CR+PR (vs. SD)	0.40	0.22–0.74	.0048			
WBC fraction	Group A (vs. others)	0.89	0.48–1.57	0.6960			
Radiation therapy	With (vs. without)	0.54	0.16–1.32	.1906	0.69	0.20–1.74	.4673
AE	With (vs. without)	1.09	0.57–1.96	0.7846			

Abbreviations: AE, adverse event; CR, complete response; LT group, patients receiving initial ICI for >1 year without progressive disease (PD); No, number; PD-L1, programmed death-ligand-1; PR, partial response; SD, stable disease; WBC, white blood cell;

[a] No patients achieving complete response or with PS ≥2 at by ICI treatment initiation showed disease progression. Therefore, the hazard ratios could not be calculated.

Table 3 Baseline and treatment characteristics of patients who were administered rechallenge treatment

Categorical data are presented as numbers (percentages) and have been compared using the X^2 and Fisher's exact tests. Continuous data are presented as medians (range) and have been compared using the Wilcoxon rank-sum test. The p value was calculated by comparing subjects in the LT and NLT groups.

	No (%)		
Characteristic	**LT group (n=10)**	**NLT group (n=27)**	***p*-value[a]**
Age, years			
Median (range)	63.5 (49–69)	67 (44–85)	0.0722
Sex			0.0149
Male	5 (50)	24 (89)	
Female	5 (50)	3 (11)	
Smoking status			0.4969
Never smoked	2 (20)	3 (11)	

Current or former smoker	8 (80)	24 (89)	
Pack-years			
Median (range)	31 (0–90)	40 (0–132)	0.6809
≥30	5 (50)	19 (70.4)	0.2553
Histology			0.2618
Adenocarcinoma	5 (50)	12 (44)	
Squamous cell carcinoma	2 (20)	13 (48)	
Non-small cell lung carcinoma	1 (10)	1 (4)	
Large cell carcinoma	1 (10)	0 (0)	
Others	1 (10)	1 (4)	
Driver mutation			0.2745
EGFR sensitizing mutation	0 (0)	0 (0)	
ALK translocation	0 (0)	0 (0)	
ROS1	1 (10)	0 (0)	
BRAF	0 (0)	1 (4)	
Others	0 (0)	1 (4)	
Not investigated	9 (90)	25 (93)	

PD-L1 status (22C3 IHC)			0.4279
<1%	0 (0)	3 (11)	
1-49%	1 (10)	5 (19)	
≥50%	4 (40)	10 (37)	
Unknown	5 (50)	9 (33)	
Response of prior ICI treatment			0.1252
CR	0 (0)	1 (4)	
PR	8 (80)	13 (48)	
SD	2 (20)	7 (26)	
PD	0 (0)	6 (22)	
Reason of prior ICI therapy discontinuation			0.4211
PD	7 (70)	15 (56)	
Other than PD	3 (30)	12 (44)	
Time to progression after first ICI therapy			0.4211
<3 months	7 (70)	15 (56)	
≥3 months	3 (30)	12 (44)	
Drug used in the rechallenge treatment			0.4168

Nivolumab	1 (10)	9 (33)	
Pembrolizumab	3 (30)	8 (30)	
Atezolizumab	6 (60)	10 (37)	
Whether ICI drug was changed from initial therapy			0.073
Yes (anti-PD-1 to anti-PD-L1)	2 (20)	14 (52)	
No	8 (80)	13 (48)	

Abbreviations: CR, complete response; ICI, immune checkpoint inhibitor; NE, not evaluable; No, number; PD, progressive disease; PD-L1, programmed death-ligand-1; PR, partial response; SD, stable disease; WBC, white blood cell.

[a] $p < .05$ was considered statistically significant.

Figure Legends

Figure 1 Progression-free survival and overall survival in the LT and the NLT groups

Kaplan–Meier curves of (A) progression-free survival and (B) overall survival according to the duration of ICI therapy.

Abbreviations: LT group, patients receiving initial ICI for >1 year without progressive disease (PD); NLT group, patients other than LT group; OS, overall survival; PFS, progression-free survival.

Figure 2 Progression-free survival of rechallenge treatment

(A) Kaplan–Meier curves of PFSR in all patients. (B) Kaplan–Meier curves of PFSR according to the duration of ICI therapy (LT or NLT group).

Abbreviations: LT group, patients receiving initial ICI for >1 year without progressive disease (PD); NLT group, patients other than LT group; PFSR, Progression-free survival of rechallenge.

Figure 3 Time to onset of irAE leading to ICI discontinuation in the LT group

This figure shows the number of patients who discontinued ICI treatment in the LT group over time.

Abbreviations: AE, adverse event; GI, gastrointestinal; irAE, immune-related AE; LT group, patients receiving initial ICI for >1 year without progressive disease (PD)

List of Supplementary Information:

Table S1 Treatment response in the LT and NLT groups

Table S2 Univariate and multivariate analyses of PFS in all patients

Table S3 Univariate and multivariate analyses of OS in all patients

Table S4 Univariate and multivariate analyses of OS in the LT group

Table S5 Univariate analysis of PFSR

Table S6 Frequency and time to AEs in the LT group

Figure S1 Progression-free and overall survival in all patients

(A) Kaplan–Meier curves of progression-free survival in all patients.

(B) Kaplan–Meier curves of overall survival in all patients.

Figure S2 Treatment response in the LT and NLT groups

Abbreviations: CR, complete response; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; NE, not evaluable; NLT group, patients other than LT group; PD, progressive disease; PR, partial response; SD, stable disease.

Figure S3 Progression-free survival in all patients by subgroup analysis

Kaplan–Meier curves of progression-free survival in all patients according to (A) sex, (B) age, (C) smoking status, (D) pack year, (E) TNM stage, (F) tumor burden, (G) irradiation, (H) performance status, (I) PD-L1 expression, (J) peripheral blood marker group, (K) response, (L)

AE. Abbreviations: AE, adverse event; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; WBC, white blood cell.

Figure S4 Overall survival in all patients by subgroup analysis

Kaplan–Meier curves of overall survival in all patients according to (A) sex, (B) age, (C) smoking status, (D) pack year, (E) TNM stage, (F) tumor burden, (G) irradiation, (H) performance status, (I) PD-L1 expression, (J) peripheral blood marker group, (K) response, (L) AE. Abbreviations: AE, adverse event; CR, complete response; NE, not evaluable; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; WBC, white blood cell.

Figure S5 Progression-free survival in the LT group by subgroup analysis

Kaplan–Meier curves of progression-free survival in the LT group according to (A) sex, (B) age, (C) smoking status, (D) pack year, (E) TNM stage, (F) tumor burden, (G) irradiation, (H) performance status, (I) PD-L1 expression, (J) peripheral blood marker group, (K) response, (L) AE. Abbreviations: AE, adverse event; CR, complete response; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; NE, not evaluable; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease; WBC, white blood cell.

Figure S6 Overall survival in the LT group by subgroup analysis

Kaplan–Meier curves of overall survival in the LT group according to (A) sex, (B) age, (C) smoking status, (D) pack year, (E) TNM stage, (F) tumor burden, (G) irradiation, (H) performance status, (I) PD-L1 expression, (J) peripheral blood marker group, (K) response, (L) AE. Abbreviations: AE, adverse event; CR, complete response; LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; NE, not evaluable; PD, progressive disease; PR, partial response; PS, performance status; SD, stable disease.

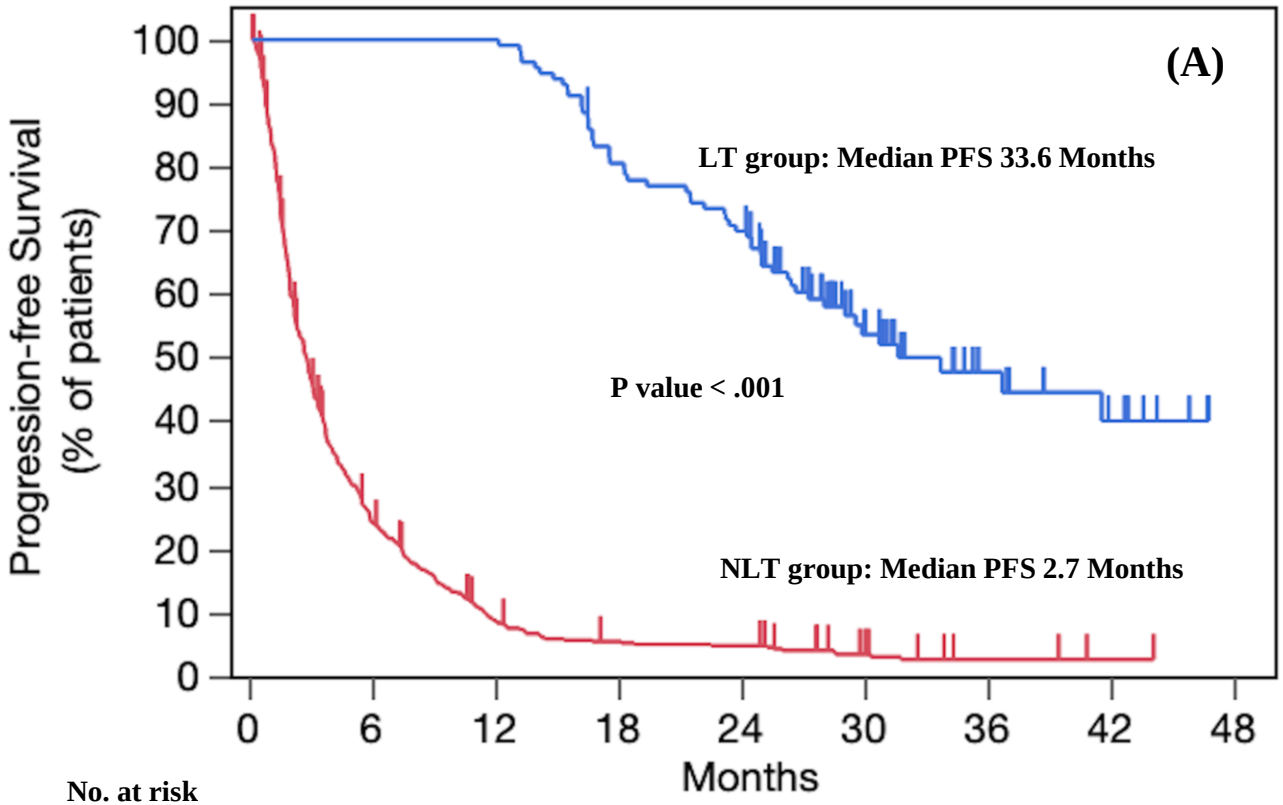
Figure S7 Progression-free survival in the LT group calculated from 1 year / 1.5 years / 2 years after ICI treatment initiation

Kaplan–Meier curves of progression-free survival at (A) 1 year / (B) 1.5 years / (C) 2 years after the start of ICI treatment. (D) The 6-month PFS rates at 1 year / 1.5 years / 2 years after the start of ICI treatment were 79.8%, 89.5%, and 80.2%, respectively. The 1-year PFS rates at 1 year / 1.5 years / 2 years after the start of ICI treatment were 69.9%, 72.2%, and 76.5%, respectively. Abbreviations: LT group, patients receiving initial immune checkpoint inhibitor for >1 year without progression disease; ICI, immune checkpoint inhibitor; PFS, progression-free survival.

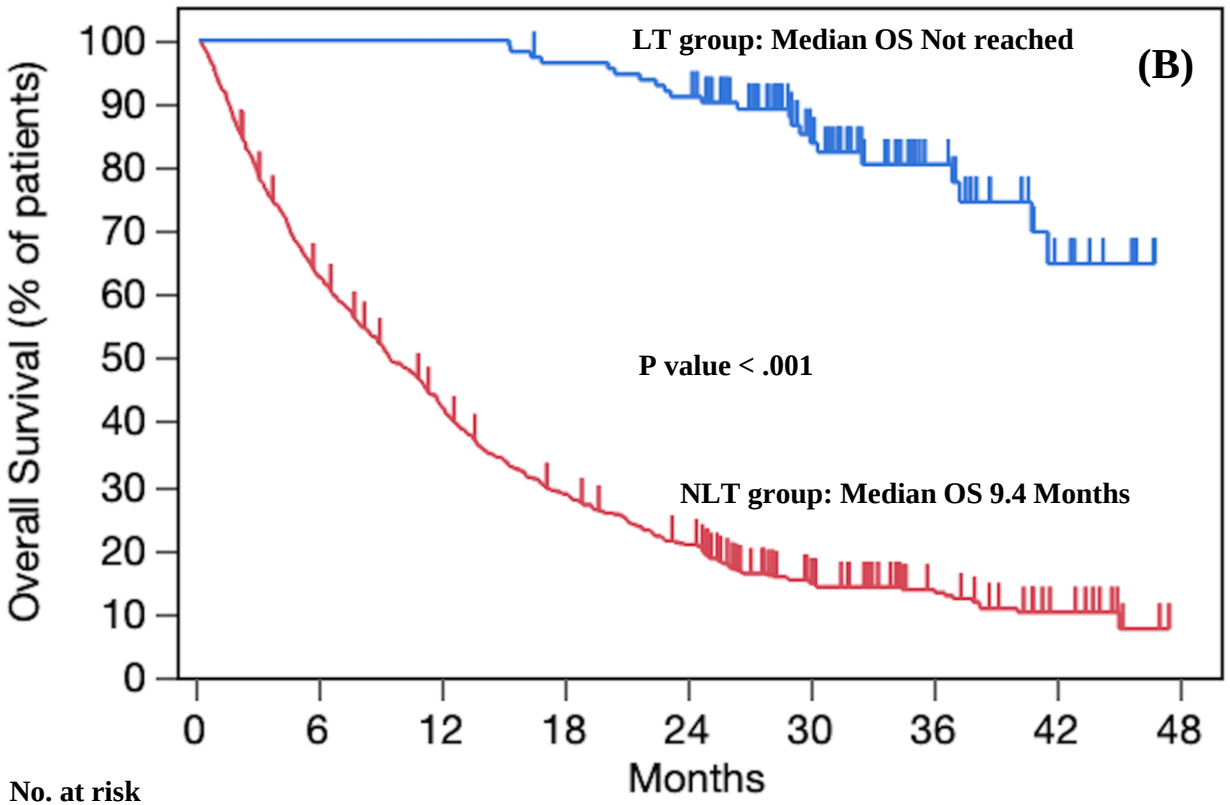
Figure S8 Overall survival in all patients who were administered rechallenge treatment

Kaplan–Meier curves of overall survival in all patients from the start of rechallenge treatment.

FIGURE 1

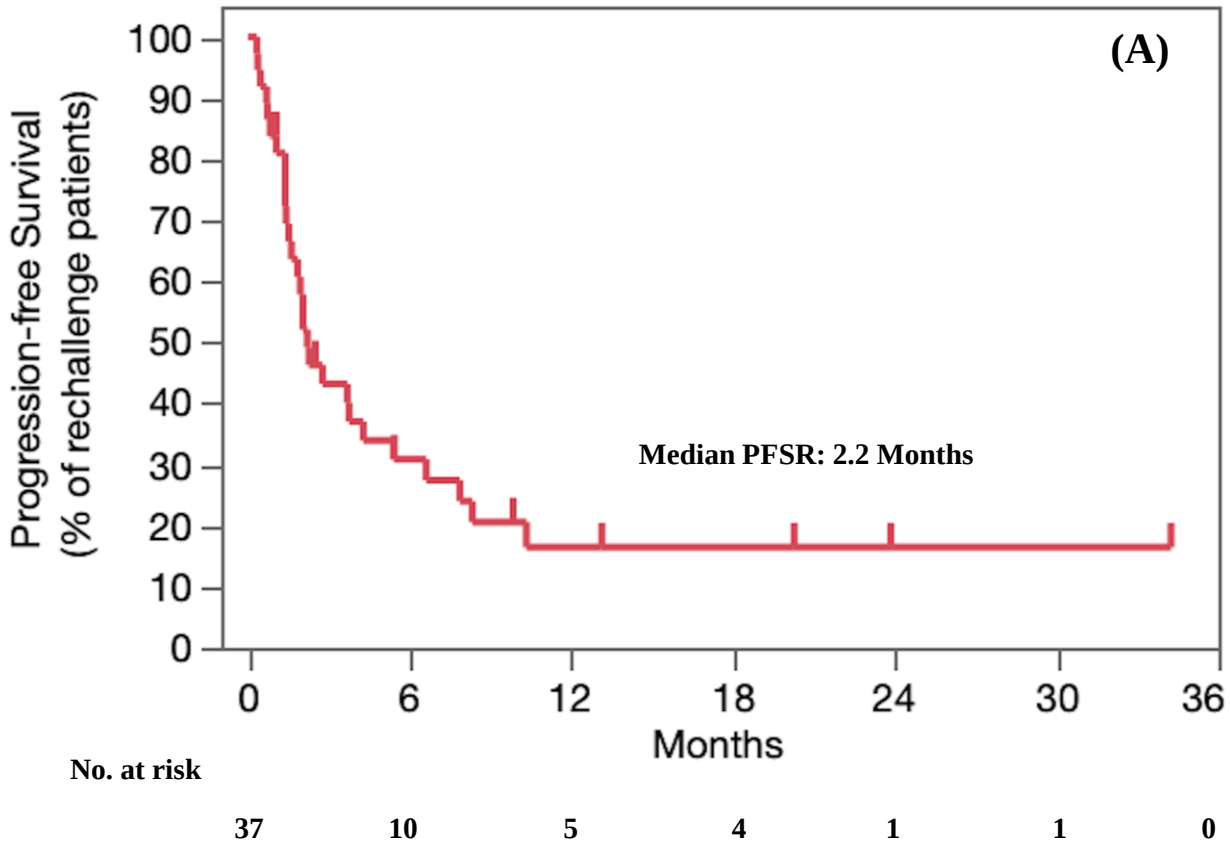


No. at risk									
LT group	114	114	114	92	80	35	17	9	0
NLT group	562	128	44	27	24	11	4	2	0



No. at risk									
LT group	114	114	114	110	104	60	32	13	0
NLT group	562	349	231	156	111	55	30	11	0

FIGURE 2


(A)
Progression-free Survival
(% of rechallenge patients)
100
90
80
70
60
50
40
30
20
10
0
Median PFSR: 2.2 Months
0
6
12
18
24
30
36
Months
No. at risk
37
10
5
4
1
1
0

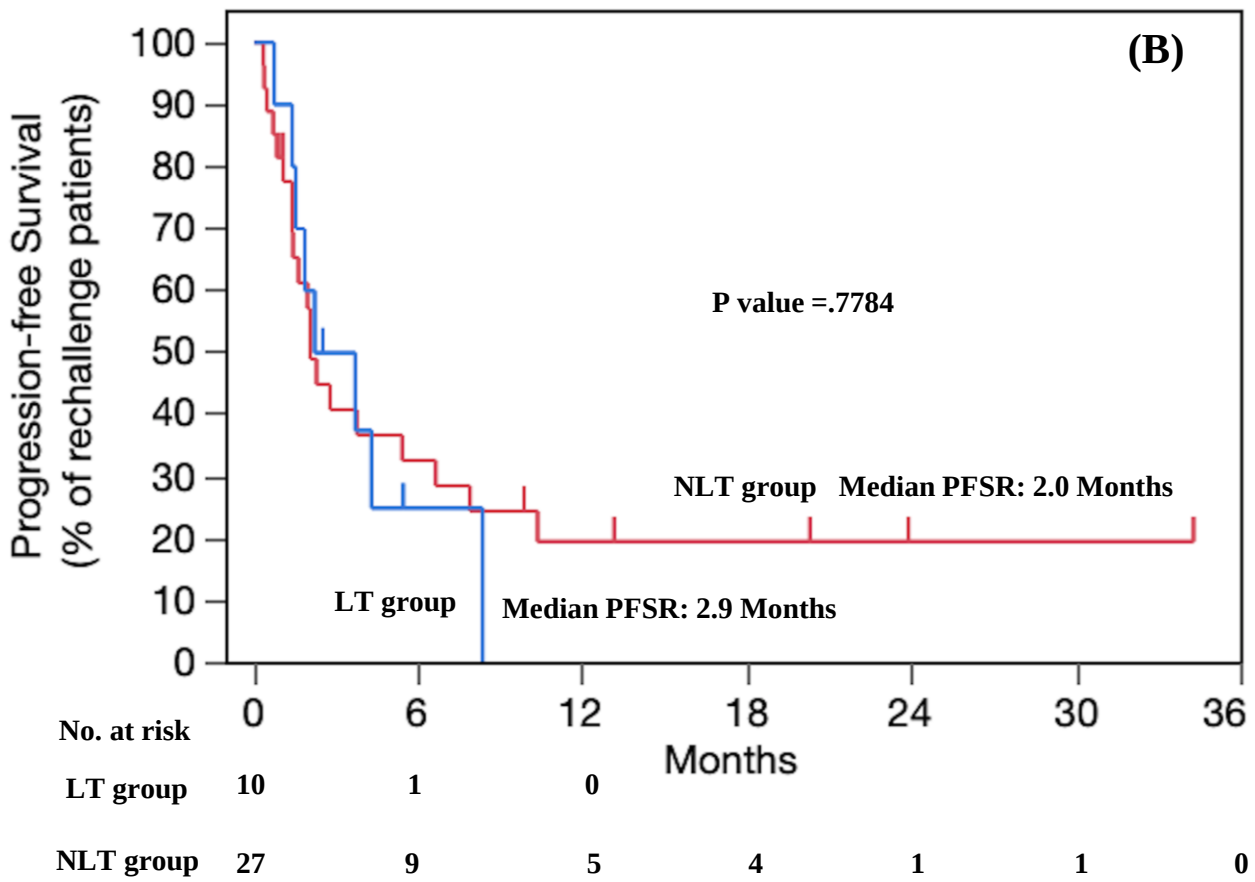
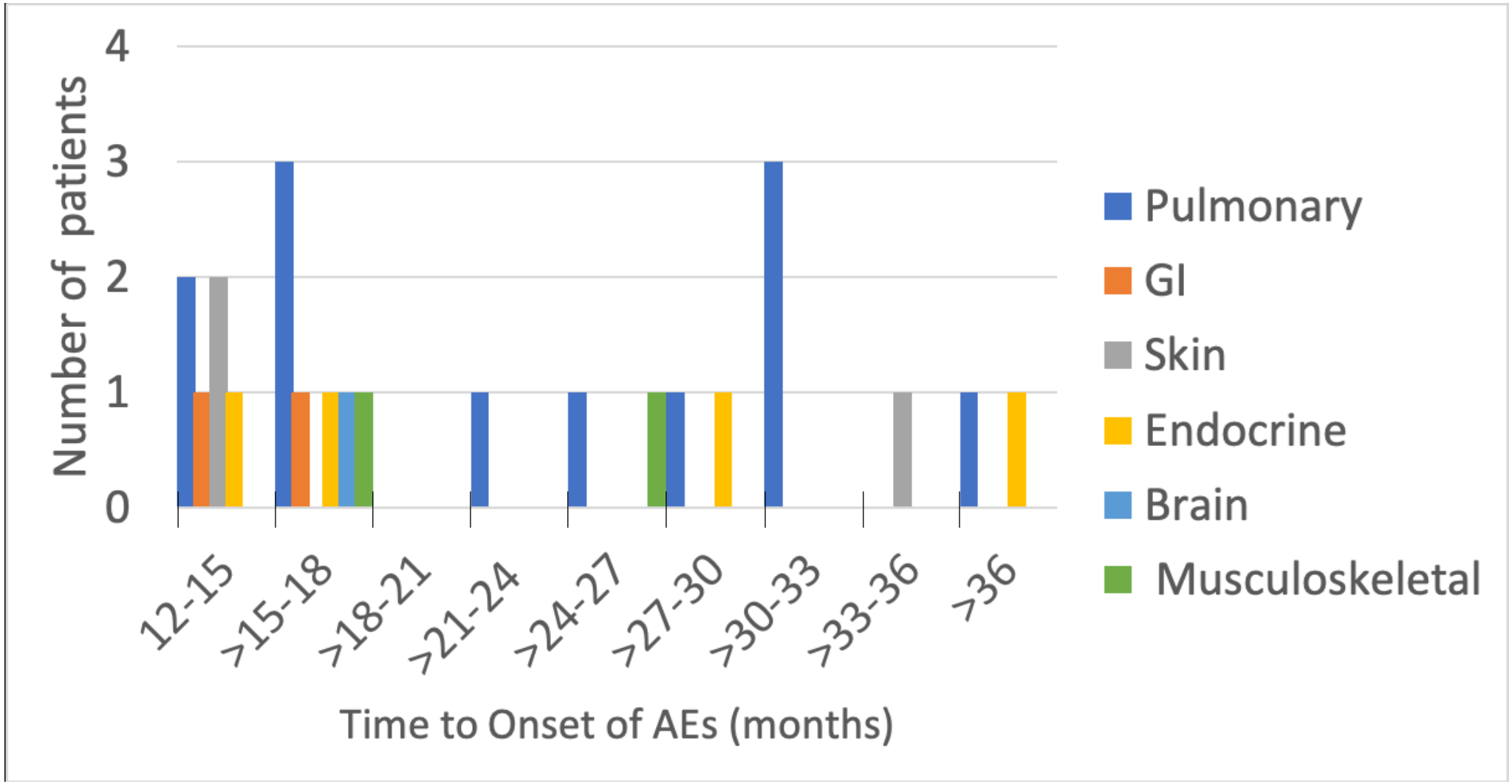

(B)
Progression-free Survival
(% of rechallenge patients)
100
90
80
70
60
50
40
30
20
10
0
P value =.7784
NLT group
Median PFSR: 2.0 Months
LT group
Median PFSR: 2.9 Months
0
6
12
18
24
30
36
Months
No. at risk
LT group 10 1 0
NLT group 27 9 5 4 1 1 0

FIGURE 3


Number of patients
4
3
2
1
0
12-15
>15-18
>18-21
>21-24
>24-27
>27-30
>30-33
>33-36
>36
Time to Onset of AEs (months)
Pulmonary
GI
Skin
Endocrine
Brain
Musculoskeletal