Association of Immune-Related Adverse Events and Efficacy Outcomes with Consolidation Pembrolizumab after Chemoradiation in Patients with Inoperable Stage III Non-small Cell Lung Cancer.

Authors: Nikhil Shukla, Sandra Althouse, Zachary Meyer, Nasser Hanna, and Greg Durm

Abstract

Background: Many patients with NSCLC treated with immunotherapy experience immune-related adverse events (irAEs). Patients with metastatic NSCLC who receive checkpoint inhibitors (CPI) and experience irAEs generally receive fewer cycles of CPI without decreased efficacy. However, the association between irAEs and efficacy outcomes in patients with locally advanced NSCLC treated with curative intent with CPI following chemoradiation has never been reported. Here we report a retrospective analysis of the association between irAEs and efficacy outcomes from the Hoosier Cancer Research Network (HCRN) LUN 14-179 single arm phase II trial of consolidation Pembrolizumab following chemoradiation in patients with stage III NSCLC.

Materials and Methods: A total of 92 eligible patients were enrolled from March 2015 to November 2016. Demographics, disease characteristics, and number of Pembrolizumab cycles received were reported in patients with and without irAEs. Chi-square test was used for comparisons for categorical variables and Wilcoxon test for continuous variables. The Kaplan-Meier method was used to analyze time to metastatic disease or death (TMDD), progression free survival (PFS), and overall survival (OS). A log-rank test was used to compare groups.

Results: Any grade irAEs occurred in 55.4% of patients. There was no significant difference in number of Pembrolizumab cycles received, TMDD, OS, or PFS in patients with and without irAEs. Patients who discontinued Pembrolizumab early due to irAEs received significantly fewer number of cycles of Pembrolizumab (5 vs 15, p=0.0016) without a significant difference in TMDD, PFS, or OS. Similarly, patients who received immunosuppressive therapy received fewer number of cycles of Pembrolizumab (4 vs 16, p <0.001) without significantly reduced TMDD, PFS, or OS.

Conclusions: irAEs due to Pembrolizumab, regardless of the grade or number of irAEs, were not associated with decreased efficacy outcomes. Furthermore, early discontinuation of Pembrolizumab due to irAEs and/or treatment of irAEs with immunosuppressive therapy was not associated with a decrease in treatment efficacy.

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Introduction

Non-small cell lung cancer (NSCLC) accounts for approximately 85% of newly diagnosed lung cancers and a third of patients will present with inoperable, locally advanced (stage III) disease at the time of diagnosis (1). The treatment for patients with unresectable stage III NSCLC had steadily evolved from radiation alone to sequential and then concurrent chemoradiation (CRT) with long term survival plateauing at approximately 20% (2,3). In the last five years, consolidation therapy with checkpoint inhibitors following chemoradiation has resulted in unprecedented increases in efficacy outcomes. The recently reported PACIFIC trial compared up to one year of consolidation therapy with the PD-L1 inhibitor Durvalumab to placebo following CRT in patients with locally advanced NSCLC and demonstrated a significant increase in progression free survival (PFS) and 3-year overall survival (OS) (4,5).

Despite improvements in efficacy outcomes, the use of checkpoint inhibitor consolidation therapy in this patient population has led to new treatment-related challenges. While treatment with PD-1 or PD-L1 inhibitors is generally well tolerated, not all patients are able to complete 1 year of consolidation therapy, and some patients may experience treatment toxicity and immune-related adverse events (irAEs). Previous studies have reported the incidence of any grade irAEs in patients with advanced cancers treated with PD-1 or PD-L1 inhibitors to be approximately 40% (6,7). As irAEs can lead to significant morbidity and mortality, promptly identifying symptoms and initiating treatment with corticosteroids or other immunosuppressive agents is critically important. Furthermore, it is general expert consensus that in patients who experience grade ≥ 2 irAEs, checkpoint inhibitor treatment should be withheld until symptoms are grade 1 or less (8).

As clinically significant irAEs require checkpoint inhibitor treatment interruption or in some cases discontinuation, there has been much interest in evaluating the association between irAEs and efficacy outcomes. Multiple retrospective studies have reported improved treatment efficacy in patients with metastatic NSCLC, melanoma, gastric cancer, and renal cell cancer who experience irAEs while being treated with checkpoint inhibitors (9-14), and there is emerging evidence that iRAEs may serve as a prognostic biomarker for treatment response. However, how irAEs impact treatment efficacy in patients with inoperable stage III NSCLC treated with consolidation immunotherapy after CRT has never been evaluated.

In this article, we report the association between irAEs and efficacy outcomes in patients treated as a part of the Hoosier Cancer Research Network (HCRN) LUN 14-179 trial, a single arm phase II trial which evaluated safety and efficacy of consolidation Pembrolizumab after CRT in patients with unresectable stage III NSCLC (15).

Methods

Trial Design

Patients with histologically confirmed inoperable stage III NSCLC were enrolled onto the trial. All patients received concurrent chemoradiation with either cisplatin/etoposide, cisplatin/pemetrexed (non-squamous NSCLC only), or carboplatin/paclitaxel and a standard dose of radiation between 59.4-66.6 Gray. Patients who exhibited no progressive or metastatic disease on imaging 4-8 weeks following completion of CRT were enrolled onto the study and treated with Pembrolizumab 200 mg IV every 3 weeks for up to one year. The primary endpoint was time to metastatic disease or death (TMDD). Secondary endpoints included PFS, OS, toxicity, and feasibility.

Patients and irAES

A retrospective review of the irAEs and efficacy outcomes from the LUN 14-179 single arm phase II trial was performed. Patient demographics, disease characteristics, and number of Pembrolizumab cycles received were evaluated in patients with and without any grade iRAEs (except grade 1 pneumonitis, which was not included). irAEs were identified as immune mediated events determined by the treating physician to be most likely due to Pembrolizumab treatment. These included any grade colitis, dermatitis, elevated transaminases, arthritis, immune thrombocytopenia, hypothyroidism, hyperthyroidism, and grade ≥ 2 pneumonitis.

Statistical Analysis

The demographics, disease characteristics and number of cycles of Pembrolizumab received in patients with and without irAEs were compared using Chi-square test (or Fisher's Exact test) for categorical variables and the Wilcoxon test for continuous variables.

The Kaplan-Meier method was used analyze TMDD, PFS, and OS. For TMDD, patients who did not have distant metastases or die were censored at their last radiological imaging. For PFS, patients who did not have disease progression or die were censored at their last radiological imagine. For OS, patients who did not die were censored at their last known alive date. Median (in months) with 95% confidence intervals were calculated for the efficacy analyses. Comparisons were made between patients with and without irAEs using the Log-rank p-value.

Results

Patient Characteristics and Incidence of irAEs

Between March 2015 and November 2016, a total of 93 patients were enrolled and received at least one cycle of Pembrolizumab. One patient was determined to be ineligible after receiving Pembrolizumab and was not included in the efficacy analysis. The primary endpoint of the original study was TMDD with the hypothesis that consolidation Pembrolizumab would improve TMDD from a historical control of 12 months to 18 months (15). Patient demographics and disease characteristics for 92 patients included in the efficacy analysis are summarized in **Table 1.**

Any grade irAES (excluding grade 1 pneumonitis) occurred in 55.4% (n=51) of patients. Reported irAEs include colitis 3.2% (n=3), dermatitis 18.5% (n=17), elevated transaminases 9.8% (n=9), arthritis 2.2% (n=2), immune thrombocytopenia 1.1% (n=1), hypothyroidism 14.1% (n=13), hyperthyroidism 10.9% (n=10), and grade ≥ 2 pneumonitis 18.5% (n=17) and are summarized in **Table 2.** A total of 20 patients experienced 2 or more irAEs. Of the 18 patients who experienced pneumonitis, 12 patients (13%) experienced grade 2 pneumonitis, 4 patients (4.3%) experienced grade 3 pneumonitis, and 1 patient (1.1%) experienced grade 4 pneumonitis. There was one pneumonitis related death For patients who experienced grade ≥ 2 pneumonitis, median time of onset after completion of radiation and start of Pembrolizumab was 112 days (range 58-394 days) and 59 days (range 8-345 days), respectively.

Association of irAEs, Efficacy Outcomes, and Duration of Consolidation Pembrolizumab

The median number of cycles of Pembrolizumab in patients with and without irAEs was 15 (range 2-19) and 12 (range 1-18), respectively (**Table 3**). The Kaplan-Meier estimates for TMDD (median 37.7 vs 22.4 months, p=0.4804) , PFS (median 25.9 vs 15.0 months, p=0.2704), and OS (median 43.1 vs 24.2 months, p=0.4126) in patients with and without any grade irAEs (excluding grade 1 pneumonitis) are shown in

Figures 1. The estimates for median TMDD, PFS, and OS for patients with 1 irAE, 2 or more iRAEs, grade 1-2 irAEs, and grade 3-4 irAEs are shown in **Table 4**.

A total of 13 patients had to discontinue Pembrolizumab consolidation early due irAEs. Median number of cycles of Pembrolizumab for patients who had to discontinue consolidation therapy vs patients who did not discontinue consolidation therapy due to irAEs was 5 (range 2-16) and 15 (range 1-19), respectively (**Table 3**). The Kaplan-Meier estimates for TMDD (30.7 vs 36.7 months, p=0.9259), PFS (10.4 vs 20.5 months, p=0.9146) and OS (30.7 months vs 37.7 months, p=0.6899) in patients who discontinued Pembrolizumab early due to irAEs compared to those who continued Pembrolizumab are shown in **Figure 2**.

A total of 21 patients received corticosteroids and 1 patient also received infliximab for irAEs, including 80.9% (n=17) for pneumonitis, 9.5% (n=2) for elevated transaminases, 4.7% (n=1) for dermatitis, and 4.7% (n=1) for arthritis. Patients who experienced pneumonitis requiring immune suppression received a median of 55 days (range 5-153 days) of corticosteroids. Median number of cycles of Pembrolizumab for patients who received immunosuppressive therapy vs patients who received no immune suppression was 4 (range 1-18) and 16 (range 1-19), respectively (**Table 3**). The Kaplan-Meier estimates for TMDD (21.5 vs 36.7 months, p=0.6985), PFS (10.4 vs 20.9 months, p=0.6925), and OS (28.1 vs 43.1 months, p=0.4758) in patients who received immunosuppressive therapy due to irAEs compared to those who did not receive immune suppression are shown in **Figure 3**.

Discussion

Our results are the first to show the relationship between irAEs and efficacy outcomes in patients with inoperable stage III NSCLC treated with checkpoint inhibitor consolidation therapy following CRT. Pembrolizumab after CRT was well tolerated. Although 55% of patients experienced irAEs, only 13 patients had to discontinue therapy directly as a result of Pembrolizumab induced immune-mediated toxicity. The incidence of irAEs and rate of early discontinuation of CPI due to irAEs were similar to previously reported studies in patients with metastatic NSCLC (10,11,16).

The incidence of pneumonitis was of particular interest in this study. Median time to onset of pneumonitis was 59 days after the start of Pembrolizumab, which was similar to the median time to onset of pneumonitis reported from the PACIFIC trial (17) The incidence of any grade pneumonitis was lower than reported with consolidation Durvalumab per the PACIFIC trial most likely due to exclusion of grade I pneumonitis (19). Grade I pneumonitis was not included in the safety analysis as patients are asymptomatic and pneumonitis may not be readily appreciable except as an incidental finding on radiographic imaging. Development of pneumonitis was not associated with reduced efficacy outcomes.

A number of studies have demonstrated increased treatment efficacy in patients with metastatic NSCLC who experience irAEs (10-12). Our study shows that while development of irAEs did not result in improved freedom from disease progression or survival, irAEs did not have a negative impact on efficacy. Interestingly, in the 13 patients who discontinued Pembrolizumab directly due to irAEs, receiving significantly fewer median number of cycles of Pembrolizumab did not correlate with reduced survival outcomes.

Patients who experience significant irAEs due to CPI may require supplementary immunosuppressive treatment in addition to therapy cessation. Previous studies in patients with advanced malignancies have

shown that management of irAEs with immune suppression does not reduce clinical efficacy of CPI or have a significant negative effect on survival (18, 20-22). Similar to what has been reported in patients with advanced NSCLC, patients in our study who received immune suppression had significantly fewer median cycles of Pembrolizumab without a reduction in survival outcomes. Of the 51 patients who experienced irAEs, 21 patients (22.8%) required immune suppression, similar to the results reported from the PACIFIC trial (18). A total of 6 patients were re-challenged with checkpoint inhibitors after disease progression. None of these patients had stopped pembrolizumab consolidation early due to irAEs.

Limitations of this study include the retrospective nature of the analysis and relatively small sample size of the study. Additionally, this study was an ad hoc unplanned subset analysis. Compared to larger studies, the reported irAEs in our study is not representative of the breadth of possible irAEs with checkpoint inhibitors. Due to the relatively subjective nature of clinical definition of irAEs, more patients than not experienced irAEs. Patients with irAEs received more median cycles of Pembrolizumab and had numerically higher but not statistically significant efficacy outcomes. Among analyzed subgroups, the number of irAEs (1 vs ≥ 2) or the grade of the irAEs did not significantly impact efficacy outcomes. However, these observations are more likely a result of a small sample size and may not be representative of observations from larger populations.

Conclusions

Immune related adverse events were not found to be associated with a reduction in efficacy outcomes in patients with inoperable stage III NSCLC receiving Pembrolizumab following standard chemoradiation. Specifically, patients who stopped CPI early as a direct result of irAEs received significantly fewer cycles of Pembrolizumab with no significant effect on efficacy outcomes. Similarly, patients who were treated with immune suppression also received significantly fewer cycles of Pembrolizumab without reduced efficacy outcomes. Incidence of grade ≥ 2 pneumonitis was less than the reported rate of any grade pneumonitis from the PACIFIC trial. Median time to onset of pneumonitis after initiation of CPI therapy was comparable to the PACIFIC trial. Although more patients experienced irAEs than did not, the number of patients with irAEs who required immunosuppressive therapy was also similar to reported results from the PACIFIC trial. Based on the results of this analysis, clinicians treating patients with inoperable stage III NSCLC with CRT followed by consolidation immunotherapy should feel comfortable stopping consolidation therapy early and/or giving immune suppression for irAEs.

Acknowledgements

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Table 1: Patient Characteristics

	Total n=92	No irAEs n=41	irAEs n=51	p-value
Median Age	66.0	67.0	64.0	0.3430
Gender – n (%)				
Female	33 (35.9%)	12 (29.3%)	21 (41.2%)	0.2365
Male	59 (64.1%)	29 (70.7%)	30 (58.8%)	
Race – n (%)				
Asian	4 (4.3%)	3 (7.3%)	1 (2.0%)	0.4433
Black or African American	3 (3.3%)	1 (2.4%)	2 (3.9%)	
Unknown	1 (1.1%)	1 (2.4%)	0	
White	84 (91.3%)	36 (87.8%)	48 (94.1%)	
Ethnicity – n (%)				
Non-Hispanic	90 (97.8%)	40 (97.6%)	50 (98.0%)	1.0000
Unknown	2 (2.2%)	1 (2.4%)	1 (2.0%)	
Stage – n (%)				
IIIA	55 (59.8%)	24 (58.5%)	31 (60.8%)	0.8270
IIIB	37 (40.2%)	17 (41.5%)	20 (39.2%)	
Smoking Status – n (%)				
Current	16 (17.4%)	8 (19.5%)	8 (15.7%)	0.9244
Former	71 (77.2%)	31 (75.6%)	40 (78.4%)	
Never	5 (5.4%)	2 (4.9%)	3 (5.9%)	
Tumor Histologic Type- n (%)				
Non-squamous	51 (55.4%)	18 (43.9%)	33 (64.7%)	0.0460
Squamous	41 (44.6%)	23 (56.1%)	18 (35.3%)	

Abbreviations: irAEs = immune-related adverse events

Table 2: Immune-related Adverse Events

Adverse Event	Any Grade (%)	Grade 1-2 (%)	Grade 3 (%)	Grade 4 (%)
Arthritis	2 (2.2)	2 (2.2)	0	0
Colitis	3 (3.2)	2 (2.2)	0	1 (1.1)
Dermatitis	17 (18.5)	16 (17.4)	1 (1.1)	0
Elevated Transaminases	9 (9.8)	9 (9.8)	0	0
Hypothyroidism	13 (14.1)	12 (13.0)	1 (1.1)	0
Hyperthyroidism	10 (10.9)	10 (10.9)	0	0
Immune Thrombocytopenia	1 (1.1)	0	1 (1.1)	0
Pneumonitis*	17 (18.5)	11 (12.0)	4 (4.3)	1 (1.1)

*Grade 1 Pneumonitis not included. There was one pneumonitis related death (grade 5).

Table 3: Cycles of Pembrolizumab Received

	Cycles of Pembrolizumab Received (Median)	Median Duration of Pembrolizumab Received (Months)	*p-value
No irAEs	12	8.3	0.7964
irAEs	15	10.4	
Discontinued Pembrolizumab due to iRAes	5	3.5	0.0016
Continued Pembrolizumab	15	11.3	
Received Immunosuppressive Therapy	4	3.5	<0.0001
No Immunosuppressive Therapy	16	11.4	

Abbreviations: irAEs = immune-related adverse events
* p-value is from the Wilcoxon test comparing the number of cycles between groups.

Table 4: Efficacy Analysis by Number and Grade of irAEs

		TMDD (months)	p-value	PFS (months)	p-value	OS (months)	p-value
Number of irAEs	No irAEs	22.4	0.7277	15	0.5257	24.2	0.5300
	1 irAE	30.7		22.7		NR	
	≥ 2 irAEs	37.7		26.5		37.7	
Grade of irAEs	No irAEs	22.4	0.3690	15	0.4488	24.2	0.1484
	Grade 1-2 irAEs	37.7		28.1		NR	
	Grade 3-4 irAEs	21.5		19.4		21.5	

Abbreviations: irAEs = immune-related adverse events; TMDD = time to metastatic disease or death; PFS = progression free survival; OS = overall survival, NR = not reached

Figure 1

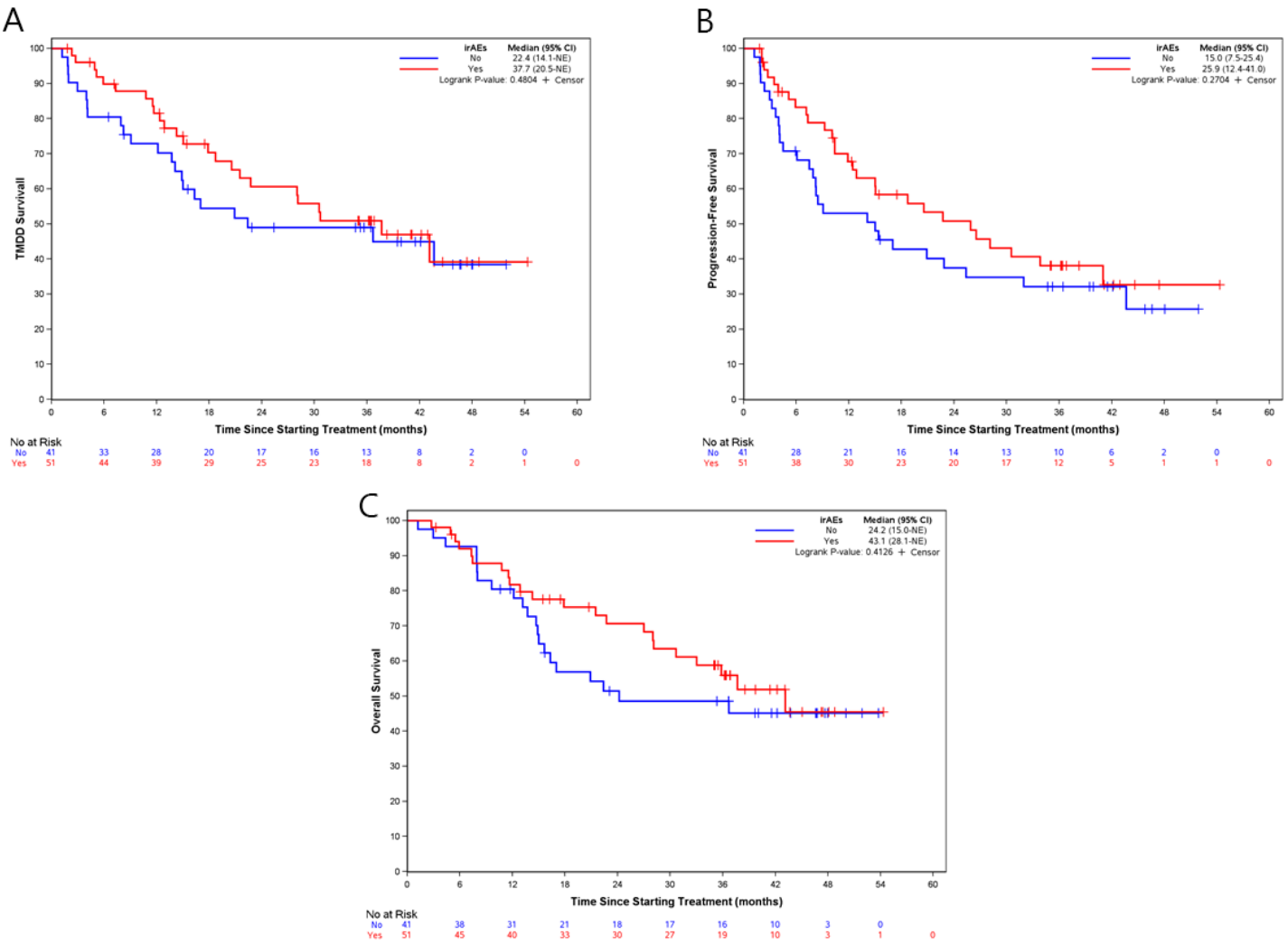

Figure 1: Kaplan-Meier curves for time to metastatic disease or death (A), progression free survival (B), and overall survival (C) in patients with and without irAEs. Patients with any grade irAEs had numerically higher median TMDD, PFS, and OS.

Figure 2

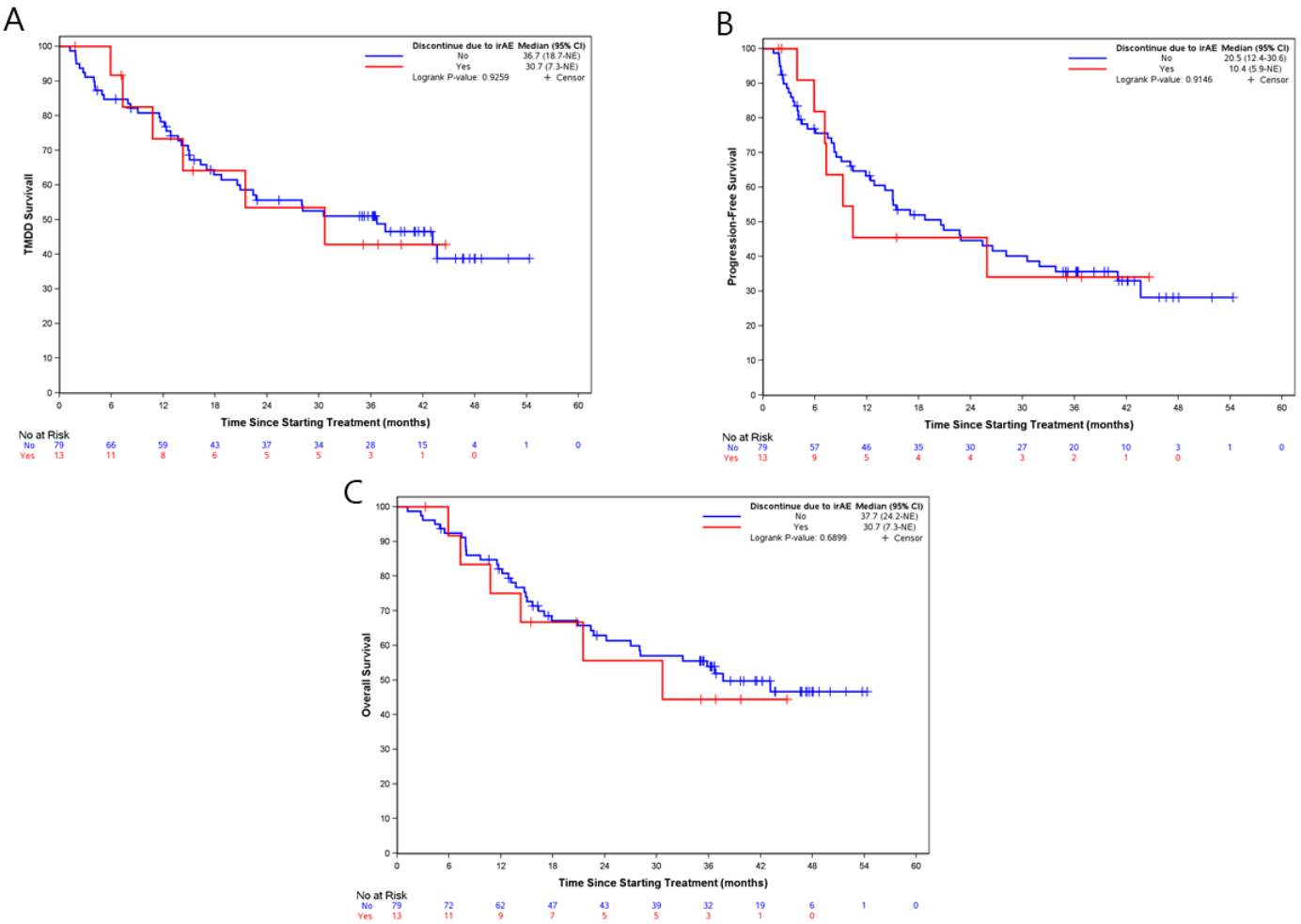

Figure 2: Kaplan-Meier curves for time to metastatic disease or death (A), progression free survival (B), and overall survival (C) in patients who stopped Pembrolizumab early due to irAEs compared to patients who continued Pembrolizumab. There was no significant difference in TMDD, PFS, or OS in patients who stopped Pembrolizumab early.

Figure 3

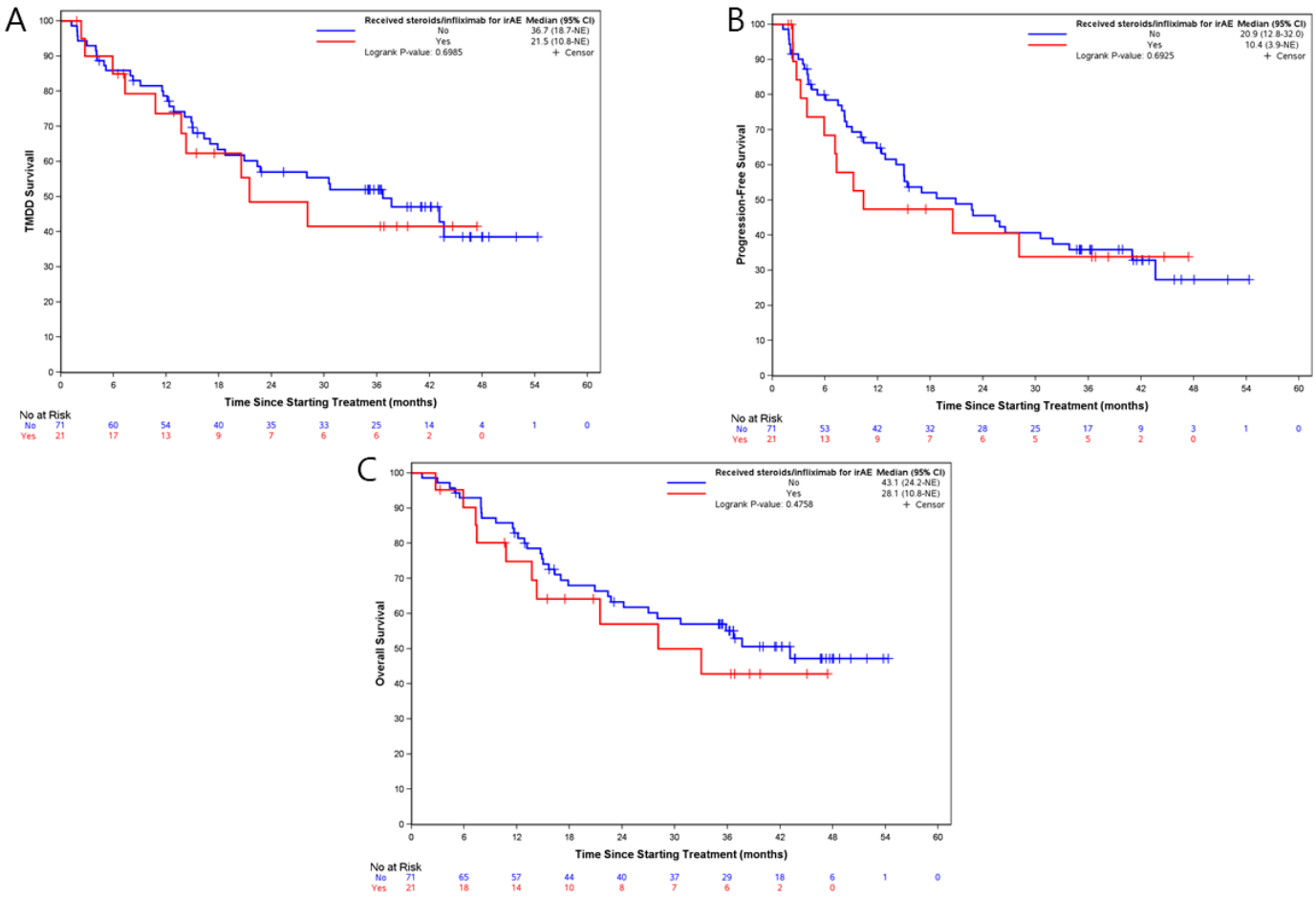

Figure 3: Kaplan-Meier curves for time to metastatic disease or death (A), progression free survival (B), and overall survival (C) in patients who received immunosuppressive agents for irAEs compared to patients who received no immunosuppressive agents. There was no significant difference in TMDD, PFS, or OS in patients who received steroids or infliximab.