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ORIGINAL ARTICLE

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African American race as a risk factor associated with a second primary lung cancer after initial primary head and neck cancer

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Abstract

Background: Initial primary head and neck cancer (IPHNC) is associated with second primary lung cancer (SPLC). We studied this association in a population with a high proportion of African American (AA) patients.

Methods: Patients with IPHNC and SPLC treated between 2000 and 2017 were reviewed for demographic, disease, and treatment-related characteristics and compared to age-and-stage-matched controls without SPLC. Logistic and Cox regression models were used to analyze the relationship of these characteristics with the development of SPLC and overall survival (OS).

Results: Eighty-seven patients and controls were compared respectively. AA race was associated with a significantly higher risk of developing SPLC (OR 2.92, 95% CI 1.35–6.66). After correcting for immortal time bias, patients with SPLC had a significantly lower OS when compared with controls (HR 0.248, 95% CI 0.170–0.362).

Conclusions: We show that AA race is associated with an increased risk of SPLC after IPHNC; reasons of this increased risk warrant further investigation.

KEYWORDS

African American, head and neck cancer, head and neck neoplasms, lung cancer, lung neoplasms

1 | INTRODUCTION

Lung cancer remains the leading cause of cancer related death in the United States.[1] Traditional risk factors for lung cancer include smoking history and exposure to second hand smoke. Current NCCN guidelines base their recommendations for lung cancer screening on age and smoking history.[2] In addition to these traditional risk factors, many studies have shown former history of cancer to be associated with development of second primary

lung cancer (SPLC).[3,4] Of these primary cancers, initial primary head and neck cancer (IPHNC) is commonly associated with SPLC.[3,4] For example, a recent retrospective study showed a rate of 6.4% for SPLC in patients with prior cancer. Nineteen percent of these patients had IPHNC with a rate of 6.7% for SPLC after IPHNC.[3] Another study showed that the standardized incidence of SPLC in patients with IPHNC far exceeded that of lung cancer in the control arm of the National Lung Screening Trial.[4] Furthermore, diagnosis of SPLC after IPHNC is associated with a significant reduction in survival.[5] The high frequency of SPLC in patients with IPHNC may be due to common risk factors such as smoking that lead to both cancers or other common risk factors not yet elucidated.

Several studies have looked at risk factors associated with SPLC after IPHNC. For example, IPHNC of supraglottic origin and lower stage IPHNC is associated with a higher risk of SPLC.[6,7] Furthermore, a history of IPHNC is associated with worse survival in SPLC compared to initial primary lung cancer.[8,9] These observations have screening and treatment implications for SPLC in patients with IPHNC. However, these studies include a small proportion of African American patients.[7,8]

We aimed to study the risk factors associated with SPLC after IPHNC. The study was conducted at Karmanos Cancer Institute., located in downtown Detroit where the resident population is 78% African American.[10] This provided us the unique opportunity to a patient population with a large proportion of African American patients. In this study, we identified patients from the Karmanos Cancer Registry with IPHNC who developed SPLC and matched them with age and stage-based controls to identify the risk factors associated with SPLC.

2 | MATERIALS AND METHODS

This was a retrospective, single center, case–control study of patients with IPHNC diagnosed or treated at Karmanos Cancer Institute who developed SPLC. The institutional review board (IRB) approved the study for the duration of its completion.

2.1 | Patient selection

Patients with IPHNC diagnosed or treated at Karmanos Cancer Institute between 2000 and 2017 were identified from the Karmanos Cancer Registry. The Karmanos Cancer Registry uses abstracted and coded data using Surveillance Epidemiology and End Results (SEER) guidelines regarding patient characteristics, cancer diagnosis, treatment, and patient outcomes. Laryngeal, oropharyngeal, hypopharyngeal, oral cavity, and other unspecified head and neck cancers with squamous cell histology were included in IPHNC. Patients with IPHNC and SPLC were identified, while patients with IPHNC without SPLC served as controls. SPLC was defined as lung cancer with a different pathology than the IPHNC or, if with same pathology, an anatomically, molecularly, or chronologically distinct tumor from IPHNC and considered unlikely to be a metastatic tumor from the IPHNC. The following variables were noted for both cohorts: age at diagnosis of IPHNC, sex, race, smoking history (defined as pack years where heavy smoking was defined as more than 30 pack per year), family history of cancer (first- and second-degree relatives), stage of IPHNC, treatment modality of IPHNC, and smoking status after treatment of IPHNC. Patients with SPLC were matched with their controls based on age at IPHNC and stage of IPHNC (stage 1, 2, 3, and 4 but not by stage 4a, 4b, or 4c). Seventh edition American Joint Committee on Cancer (AJCC) staging system was used.

2.2 | Statistical methods

Patient characteristics were summarized by count and percentage for categorical variables and median and range for continuous variables. Those characteristics were further compared by the status of second diagnosis using chi-square or Fisher's exact tests for categorical variables and Wilcoxon rank-sum tests for continuous variables. The time to second primary lung cancer (SPLC) was defined as the duration from the date of first diagnosis to the date of SPLC. Overall survival (OS) was defined as the duration from the date of first diagnosis to the date of death from any cause. The distributions of time to SPLC and OS were summarized by Kaplan–Meier (KM) curves and their median and 95% confidence interval (CI) were estimated by KM estimates. The univariable and multivariable logistic regression analyses were performed to compare the associations between six prechosen variables (race, smoking status after treatment, family history, smoking history at first diagnosis, stage at first diagnosis, and treatment modality) with the status of second diagnosis. Firth logistic regression models were used to reduce bias in maximum likelihood estimation caused by rare events. After including the status of second diagnosis as additional covariate, univariable and multivariable Cox regression analyses were carried out for overall survival (OS). In particular, patients who had second diagnosis must survive at least until the date of SPLC. In other words, death cannot occur until the date of SPLC to those who had second diagnosis, which is

TABLE 1 Patient characteristics

	No. of patients with SPLC, $N = 87$ (%)	No. of patients with IPHNC only, $N = 87$ (%)	All patients with IPHNC, $N = 174$ (%)	*p*-value
Age at diagnosis of IPHNC – median (range)	59 (45–87)	59 (45–88)	59 (45–88)	0.861
Sex				
Male	60 (69)	66 (76)	126 (72)	0.396
Female	27 (31)	21 (24)	48 (28)	
Race				
White	48 (55)	61 (70)	109 (63)	*0.036*
African American	39 (45)	24 (28)	63 (36)	
Missing	0 (0)	2 (2)	2 (1)	
Continued smoking after treatment of IPHNC				
Yes	44 (51)	37 (43)	81 (47)	0.318
No	40 (46)	48 (55)	88 (51)	
Missing	3 (3)	2 (2)	5 (3)	
Family history of cancer				
Yes	52 (60)	34 (39)	86 (49)	0.375
No	31 (36)	29 (33)	60 (34)	
Missing	4 (5)	24 (28)	28 (16)	
Smoking history at diagnosis of IPHNC				
Nonsmoker	2 (2)	5 (6)	7 (4)	0.440
Heavy smoker (>30 pack-year)	84 (97)	81 (93)	165 (95)	
Missing	1 (1)	1 (1)	2 (1)	
Anatomic site of IPHNC				
Oral	15 (17)	18 (21)	33 (19)	0.418
Oropharyngeal	15 (17)	18 (21)	33 (19)	
Laryngeal	40 (46)	30 (34)	70 (40)	
Hypopharyngeal	7 (8)	3 (3)	10 (6)	
Other	2 (2)	4 (5)	6 (3)	
Missing	8 (9)	14 (16)	22 (13)	
Stage of IPHNC				
1	19 (22)	19 (22)	38 (22)	*0.025*
2	45 (52)	44 (51)	89 (51)	
4a/b	22 (25)	15 (17)	37 (21)	
4c	0 (0)	8 (9)	8 (5)	
Missing	1 (1)	1 (1)	2 (1)	
Treatment modality of IPHNC				
Surgery	37 (43)	33 (38)	70 (40)	0.313
Chemo	9 (10)	17 (20)	26 (15)	
Chemoradiation	30 (34)	23 (26)	53 (30)	
Radiation	7 (8)	7 (8)	14 (8)	
Missing	4 (5)	7 (8)	11 (6)	

(Continues)

TABLE 1 (Continued)

	No. of patients with SPLC, $N = 87$ (%)	No. of patients with IPHNC only, $N = 87$ (%)	All patients with IPHNC, $N = 174$ (%)	*p*-value
Stage of SPLC				
1	41 (47)		41 (24)	NA
2	20 (23)		20 (11)	
3	5 (6)		5 (3)	
4	20 (23)		20 (11)	
Missing	1 (1)		88 (51)	

Note: *p*-values (<0.05) are marked in italics.
Abbreviations: IPHNC, initial primary head and neck cancer; SPLC, second primary lung cancer.

TABLE 2 Univariable and multivariable logistic regression analysis for risk factors associated with second primary lung cancer

	Univariable		Multivariable	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
Race				
White	Reference		Reference	
African American	2.04 (1.10–3.87)	*0.024*	2.92 (1.35–6.66)	*0.006*
Continued smoking after treatment of IPHNC				
Yes	Reference		Reference	
No	0.704 (0.38–1.28)	0.252	0.70 (0.32–1.49)	0.357
Family history of cancer				
Yes	Reference		Reference	
No	0.70 (0.36–1.36)	0.293	0.62 (0.29–1.29)	0.201
Smoking history at diagnosis of IPHNC				
Nonsmoker	Reference		Reference	
Heavy smoker (>30 pack-year)	2.28 (0.53–12.98)	0.272	2.63 (0.44–27.82)	0.304
Stage of IPHNC		0.108		0.472
1–2	Reference		Reference	
4a-b	1.43 (0.70–3.02)	0.338	0.88 (0.38–2.03)	0.757
4c	0.06 (0.00–0.48)	*0.004*	0.103 (0.01–1.41)	0.094
Treatment modality of IPHNC				
Surgery	Reference		Reference	
Nonsurgery	0.88 (0.47–1.62)	0.670	1.05 (0.49–2.25)	0.896

Note: *p*-values (<0.05) are marked in italics.
Abbreviations: CI, confidence interval; IPHNC, initial primary head and neck cancer; OR, odds ratio.

called "immortal time bias," meaning that there is an interval during which the study event cannot occur.[11] Thus, in order for OS analysis to correct the potential immortal time bias due to patients who had second diagnosis, the status of second diagnosis was considered a time-varying covariate. The proportional hazard assumption was validated and no violation was found except for the status of second diagnosis that was resolved by the time-dependent covariate. The follow-up time was calculated using the reverse KM estimate.

3 | RESULTS

3.1 | Demographics

We identified a cohort of 174 patients with IPHNC including 87 patients with SPLC and 87 controls without SPLC. The median age of diagnosis in the SPLC arm was 59 years (Table 1). Most patients with SPLC were male (69%, $n = 60$), of white race (55%, $n = 48$) and had a history of heavy smoking (97%, $n = 84$),

while 45% ($n = 39$) of patients were African American. Sixty percent ($n = 52$) of patients had a family history of cancer. Fifty-one percent ($n = 44$) of patients continued smoking after treatment for IPHNC. In patients with SPLC, most IPHNC were of the larynx (46%, $n = 40$) and were of stage 2 disease (50%, $n = 45$). Surgery was the treatment of choice in 43% ($n = 37$) of patients followed by chemoradiation in 34% ($n = 30$). Most of SPLC were of stage 1 disease (47%, $n = 41$) followed by stage 2 and stage 4 disease (23%, $n = 20$), respectively.

Patient characteristics were similar in the control group except for race and stage of IPHNC. In the control group, a greater proportion of patients were white (70%, $n = 61$) and had a higher incidence of stage 4c disease (9%, $n = 8$). Table S1, Supporting Information shows patient characteristics by race. No difference in predefined patient characteristics was seen between the two groups by race.

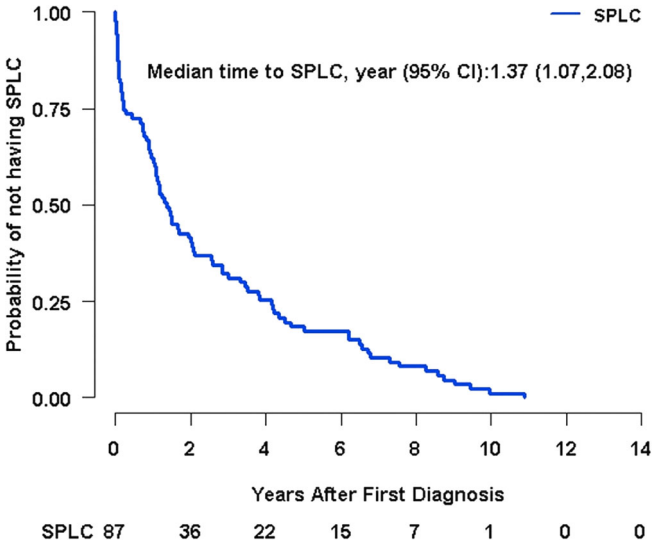

FIGURE 1 Kaplan–Meier curve of time to diagnosis of second primary lung cancer (SPLC) from initial primary head and neck cancer [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Univariable and multivariable Cox regression analysis for risk factors associated with overall survival

	Univariable		Multivariable	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**
SPLC status				
Yes	Reference		Reference	
Control (no SPLC)	0.25 (0.17–0.36)	*<0.001*	0.19 (0.12–0.30)	*<0.001*
Race				
White	Reference		Reference	
African American	1.43 (1.00–2.06)	0.052	1.36 (0.87–2.13)	0.181
Continued smoking after treatment of IPHNC				
Yes	Reference		Reference	
No	0.76 (0.52–1.10)	0.140	1.02 (0.65–1.60)	0.936
Family history of cancer				
Yes	Reference		Reference	
No	1.00 (0.65–1.47)	0.918	1.12 (0.72–1.74)	0.629
Smoking history at diagnosis of IPHNC				
Nonsmoker	Reference		Reference	
Heavy smoker (>30 pack-year)	1.65 (0.60–4.50)	0.331	0.90 (0.21–3.90)	0.890
Stage of IPHNC				
1–2	Reference		Reference	
4a-b	1.51 (0.97–2.34)	0.069	1.27 (0.77–2.08)	0.352
4c	6.42 (3.03–13.61)	*<0.001*	6.27 (1.77–21.87)	*0.004*
Treatment modality of IPHNC				
Surgery	Reference		Reference	
Nonsurgery	1.28 (0.87–1.89)	0.211	1.33 (0.84–2.10)	0.222

Note: Time-varying covariate-based correction for potential immortal time bias. *p*-values (<0.05) are marked in italics.
Abbreviations: CI, confidence interval; HR, hazard ratio; IPHNC, initial primary head and neck cancer; SPLC, second primary lung cancer.

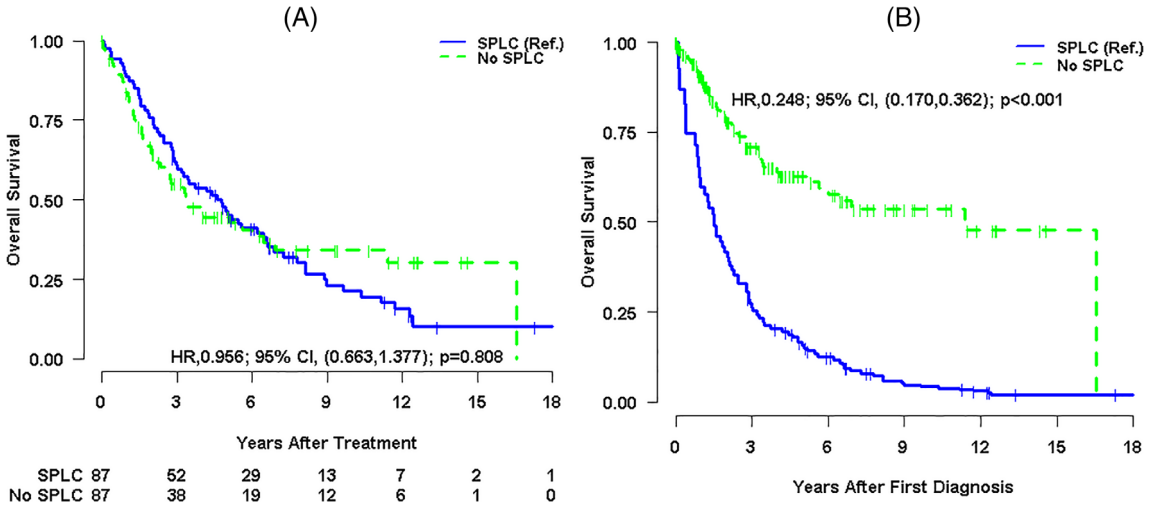

FIGURE 2 Kaplan–Meier curve of overall survival (OS) by SPLC status (A) before and (B) after correcting for immortal time bias using time-varying covariate. (A) The median OS is 4.79 years (95% CI 3.18–6.60) and 3.38 years (95% CI 2.49–6.93) for SPLC and No-SPLC, respectively. The median follow-up time of OS is 12.28 years (95% CI 11.31–NR) and 7.05 years (95% CI 4.83–11.50) for SPLC and No-SPLC, respectively. (B) The median OS is 1.49 years (95% CI 0.89–2.77) and 11.39 years (95% CI 5.99–NR) for SPLC and No-SPLC, respectively. The median follow-up time of OS is 7.51 years (95% CI 6.11–13.42) and 3.52 years (95% CI 2.83–4.52) for SPLC and No-SPLC, respectively. SPLC, second primary lung cancer

3.2 | Second primary lung cancer

African American race (Table 2) was significantly associated with SPLC when compared to white race on univariable and multivariable analysis with odd ratio of 2.04 (95% CI 1.10–3.87) and 2.92 (95% CI 1.35–6.66), respectively. Stage 4c IPHNC was associated with a significantly lower risk of SPLC when compared with stage 1 and 2 diseases on univariable analysis (OR 0.06, 95% CI 0.00–0.48). However, this difference was not seen on multivariable analysis (OR 0.10, 95% CI 0.01–1.41).

Table 3 shows univariable and multivariable cox-regression analysis of risk factors associated with OS. On univariable and multivariable analysis, SPLC diagnosis was associated with a significantly shorter OS compared with absence of SPLC with hazard ratio of 0.25 (95% CI 0.17–0.36) and 0.19 (95% CI 0.12–0.30), respectively. Stage 4c IPHNC was also associated with a significantly shorter OS when compared with stage 1 and 2 diseases on univariable and multivariable analyses with hazard ratio of 6.42 (95% CI 3.03–13.61) and 6.42 (95% CI 3.03–13.61), respectively.

3.3 | Overall survival

After a median follow-up of 1.49 years, median time to diagnosis of SPLC was 1.37 years (95% CI 1.07–2.08) (Figure 1). Patients continued to be diagnosed with SPLC until 10 years from the diagnosis of IPHNC. Figure 2A shows OS. Patients with SPLC and controls had a similar OS (HR 0.956, 95% CI 0.663–1.377) with median OS of 4.79 years (95% CI 3.18–6.6) and 3.38 years (95% CI 2.49–6.93) for patients and controls respectively. After correcting for potential immortal time bias (Figure 2B), patients with SPLC had a significantly lower OS when compared with controls (HR 0.248, 95% CI 0.170–0.362).

4 | DISCUSSION

In this study, we explored the risk factors associated with SPLC after IPHNC and found that African American race was associated with a significantly higher risk of developing SPLC. This association was also observed by Milano et al. in their analysis of the SEER database for IPHNC.[7] They extracted patients with IPHNC from the SEER registry who later developed lung cancer and aimed to analyze the long-term survival of this patient group. On univariate analysis, African American race was associated with increased risk of developing lung cancer compared to white race (5 years, 7.0% vs. 5.8%; 10 years, 14.1% vs 11.4%; 15 years, 20.2% vs. 16.4%; $p < 0.00001$). On multivariate analysis, this increased risk remained with HR 1.27 (95% CI 1.16–1.40, $p < 0.0001$). This difference in risk may be explained by genetic and epigenetic factors that seem to modify the risk of lung cancer despite similar exposure history. For example, according to the prospective data by Stram et al. obtained from MEC (multiethnic cohort study), AA race was associated with a higher excessive-relative-risk (ERR) of developing lung cancer when standardized for age and nicotine exposure.[12] This is of note since in our study African

American and white patients had a similar smoking history (Table S1). Therefore, difference in SPLC in African American and white patients in our study is not explained by nicotine exposure.

Despite the increased risk of lung cancer associated with African American race, we did not note a difference in survival by race. This may, in part, be due to improved treatment of lung cancer allowing for longer survival in these patients. Stage of lung cancer at diagnosis and type of lung cancer treatment was not analyzed which is a limitation of the study. Therefore, further conclusions cannot be made about whether early diagnosis of lung cancer in AA patients with IPHNC informs survival.

Stage 4c IPHNC was noted to be associated with a lower risk of SPLC. This can be explained by a shorter survival of patients with advanced head-and-neck cancer allowing minimal time to develop SPLC. Median OS of stage 4c head-and-neck cancer (HNC) is 1 year, while, in our study, median time from IPHNC to diagnosis of SPLC was 1.3 years. Therefore, patients with stage 4c HNC may not live long enough to develop SPLC.

Moreover, in patients with stage 4c IPHNC with a solitary lung nodule, clinicians may assume the lung nodule to be a metastasis from IPHNC and may not obtain a biopsy, potentially missing a SPLC. This may have also contributed to a higher recorded rate of stage 4c disease in our study controls as lung nodules may have gone without biopsy and assumed to represent stage 4c IPHNC. Furthermore, smoking history was not associated with increased risk of SPLC. This is likely because 95% of all patients in this study had a history of heavy smoking. A larger sample size would be needed to detect a difference in SPLC by smoking history. Smoking status at the time of IPHNC also did not inform the risk of SPLC.

Lastly, our study showed that, after correcting for immortal time bias, patients with SPLC had a significantly lower OS compared to controls. This is in line with the observation by Kim et al. and Chen et al. who showed that patients with SPLC had a significantly shorter OS compared to IPHNC patients without SPLC.[5,13] In the study by Kim et al., 33% (6/18) of patients had stage I-II NSCLC, while 50% (9/18) had stage III-IV NSCLC.[13] It may be hypothesized that stage of SPLC at diagnosis may affect the overall outcome and survival of patients with IPHNC who develop SPLC. However, this was not analyzed in our study.

5 | LIMITATIONS

This study has several limitations to consider when interpreting the results. First, this study was retrospective in its design. We attempted to mitigate this limitation using multivariable adjusted analyses and controlling for immortal time bias. Second, differentiating the diagnosis of SPLC from head-and-neck cancer with lung metastasis can be challenging. Molecular testing to differentiate squamous cell carcinoma due to SPLC versus metastatic head-and-neck cancer is an exciting potential option but not widely available.[14] Nonetheless, our study results provide important insight into the risk factors associated with the development of SPLC after IPHNC.

5.1 | Implications

Eighty-five percent of head-and-neck cancers are associated with tobacco use indicating that many patients with IPHNC will meet the criteria for routine lung cancer screening based on age and smoking history.[15] Despite the 20% reduction in lung cancer mortality with lung cancer screening, adherence to screening guidelines is estimated to be only 14%.[16,17] Furthermore, adherence with lung cancer screening guidelines is even lower in non-white individuals.[18]

Recently, the US Preventive Services Task Force recommended screening for lung cancer be extended to those at an earlier age (starting at age 50 instead of 55) and with less pack-years of smoking (20 pack-years instead of 30).[19] These new recommendations are expected to help reduce racial disparities in screening with a 107% increase in African Americans that are eligible for screening compared with a 78% increase in whites.[19] Our data show the increased risk of lung cancer in patients with head-and-neck cancer, especially in African Americans. Therefore, we recommend incorporating lung cancer screening into standard head-and-neck cancer survivorship care based on current guidelines with special focus in racial minorities.

6 | CONCLUSION

In summary, African American race is associated with an increased risk of SPLC after IPHNC. Adherence with lung cancer screening in the real world is low, especially in African Americans, and our results underscore the importance of lung cancer screening in patients with IPHNC using established guidelines.

CONFLICT OF INTEREST

Dr. Ammar Sukari serves on the advisory board for Merck and Eisai. He has received study funding from Eisai. Dr. Misako Nagasaka serves on the advisory board for AstraZeneca, Caris Life Sciences, Daiichi-Sankyo, Takeda, Novartis, EMD Serono and has received study

funding from Tempus. Dr. Misako Nagasaka has been awarded the 2020 Karmanos Cancer Institute Cancer Immunology and Immunotherapy Pilot Award (P30 CA022453). All other authors have no potential conflict of interest to declare.

DATA AVAILABILITY STATEMENT

De-identified data may be made available upon request to the corresponding author.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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