Five-Year Clinical Outcomes after Neoadjuvant Nivolumab in Resectable Non–Small Cell Lung Cancer

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ABSTRACT

Purpose: Neoadjuvant anti–PD-1 therapy has shown promise for resectable non–small cell lung cancer (NSCLC). We reported the first phase I/II trial of neoadjuvant nivolumab in resectable NSCLC, finding it to be safe and feasible with encouraging major pathological responses (MPR). We now present 5-year clinical outcomes from this trial, representing to our knowledge, the longest follow-up data for neoadjuvant anti–PD-1 in any cancer type.

Patients and Methods: Two doses of nivolumab (3 mg/kg) were administered for 4 weeks before surgery to 21 patients with Stage I–IIIA NSCLC. 5-year recurrence-free survival (RFS), overall survival (OS), and associations with MPR and PD-L1, were evaluated.

Results: With a median follow-up of 63 months, 5-year RFS and OS rates were 60% and 80%, respectively. The presence of MPR and pre-treatment tumor PD-L1 positivity (TPS ≥1%) each trended toward favorable RFS; HR, 0.61 [95% confidence interval (CI), 0.15–2.44] and HR, 0.36 (95% CI, 0.07–1.85), respectively. At 5-year follow-up, 8 of 9 (89%) patients with MPR were alive and disease-free. There were no cancer-related deaths among patients with MPR. In contrast, 6/11 patients without MPR experienced tumor relapse, and 3 died.

Conclusions: Five-year clinical outcomes for neoadjuvant nivolumab in resectable NSCLC compare favorably with historical outcomes. MPR and PD-L1 positivity trended toward improved RFS, though definitive conclusions are limited by cohort size.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide (1). For patients with resectable disease, 5-year survival rates can range from 68%, for stage IB, to 36% for IIIA disease (2). Despite advances in treatments for advanced non–small cell lung cancer (NSCLC), breakthroughs have only recently emerged for early-stage disease (3–5). Results and overall survival (OS) from studies evaluating immune checkpoint blockade (ICB) in the peri-operative setting are still maturing.

Our group published the first clinical trial of neoadjuvant anti-programmed-cell death protein-1 (PD-1) therapy in any cancer type,

finding it to be safe and feasible (6), with informative immunologic correlative follow-up data (7). In the current report, we present final clinical results from this study, representing, to our knowledge, the longest follow-up data for neoadjuvant anti–PD-1 therapy. In addition to long-term clinical outcomes, we present data on key subgroups, providing insight to researchers and clinicians navigating this rapidly evolving treatment setting.

Patients and Methods

Patient selection and study design

This open-label single-arm phase Ib/II study (NCT02259621) was conducted at Johns Hopkins University and Memorial Sloan-Kettering Cancer Center. Patients, ages ≥18 years, with resectable stage I (>4 cm)–IIIA NSCLC, were eligible. Staging was per American Joint Committee on Cancer 7th edition (8). Additional eligibility criteria have been reported (6).

Enrolled patients received two pre-operative doses of intravenous nivolumab (3 mg/kg of body weight) every 2 weeks. Surgical resection was planned approximately 4 weeks after the first dose.

This clinical trial and research study were conducted in accordance with the U.S. Common rule. Informed written consent was obtained from each subject or each subject's guardian prior to clinical trial enrollment. All human investigations were performed after approval by an institutional review board in accordance with an assurance filed with and approved by the U.S. Department of Health and Human Services.

Study endpoints and biomarkers

Primary endpoints of this study were safety and feasibility both having been previously reported (6). This analysis is a description of five-year outcomes for all patents who successfully underwent definitive resection of their disease after neoadjuvant nivolumab. Key exploratory endpoints included pathological markers of response and

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Translational Relevance

Neoadjuvant immune checkpoint blockade is increasingly being incorporated into the perioperative treatment setting for solid tumor malignancies, including resectable non–small cell lung cancer (NSCLC). However, long-term outcomes, specifically survival, after treatment with these agents are still maturing. In this report, we present the five-year clinical outcomes after neoadjuvant nivolumab for resectable NSCLC, representing, to our knowledge, the longest follow-up data available after neoadjuvant anti–PD-1 therapy in any cancer type. In addition to the durable clinical benefit of neoadjuvant nivolumab highlighted in this report, the examination of key subgroups and biomarkers may help clinicians and investigators as they look to navigate this rapidly evolving treatment landscape. Several questions still remain on how to further optimize perioperative outcomes for patients with resectable NSCLC, making long-term follow-up data, as reported here, particularly valuable.

Table 1. Demographic data for all enrolled patients ($n = 21$) at baseline and based on pathological response ($n = 20$).

Characteristic	All Patients ($N = 21$)	Patients with MPR ($N = 9$)	Patients without MPR ($N = 11$)
Median age at enrollment, years (range)	67 (55–84)	66 (57–79)	67 (55–84)
Sex, number (%)			
Female	11 (52)	6 (67)	4 (36)
Male	10 (48)	3 (33)	7 (64)
Histology, number (%)			
Adenocarcinoma	13 (62)	6 (67)	6 (55)
Squamous cell carcinoma	6 (29)	2 (22)	4 (36)
Other[a]	2 (10)	1 (11)	1 (9)
Clinical stage at diagnosis[b], number (%)			
I	4 (19)	2 (22)	2 (18)
II	10 (48)	5 (56)	5 (45)
IIIA	7 (33)	2 (22)	4 (36)
Smoking status, number (%)			
Never	3 (14)	1 (11)	2 (18)
Former or Current	18 (86)	8 (89)	9 (82)
PD-L1 status[c] (%)			
≥1%	7 (33)	3 (33)	4 (36)
<1%	8 (38)	2 (22)	6 (55)
N/A	6 (29)	4 (44)	1 (9)
Adjuvant Treatment (%)			
Yes	6 (29)	2 (22)	4 (36)
No	15 (71)	7 (78)	7 (64)

Note: One patient was deemed unresectable at time of surgery, without evaluable pathological response.

Abbreviations: MPR, Major pathological response; %, Percentage; PD-L1, Programmed death-ligand 1; N/A, Not available.

[a]Other histologic diagnoses included pleomorphic and adenosquamous carcinomas.

[b]Clinical staging was per American Joint Committee on Cancer Tumor Node Metastases 7th edition.

[c]On the basis of pre-treatment tumor PD-L1 expression (TPS < 1% vs. ≥1%). There were 5 patients where pre-treatment PD-L1 assessment was not available (N/A).

assessments of recurrence-free survival (RFS) and OS, measured from date of surgery. Pathological response was measured as the percentage of residual viable tumor (%RVT) identified on routine hematoxylin and eosin staining (9). Pathological complete response (pCR) and major pathological response (MPR) were defined as 0% and ≤10% residual viable tumor, respectively. IHC was performed for pretreatment tumor PD-L1 evaluation. PD-L1 staining was performed on formalin-fixed, paraffin-embedded (FFPE) tissue sections using the Dako PD-L1 IHC 28–8 pharmDx assay. Samples were considered to be PD-L1$^+$ if ≥1% of tumor cells showed membranous PD-L1 expression.

For the 11 patients with tumor samples available for sequencing analysis, correlations between mean tumor mutational burden (TMB) and RFS/OS were assessed. Whole-exome sequencing was performed on pre-treatment tumor and matched normal samples. FFPE tumor samples underwent pathological review for confirmation of diagnosis and tumor purity assessment. Qiagen DNA FFPE and Qiagen DNA blood mini kit was used to extract DNA from patients' tumors and matched peripheral blood, respectively. VariantDx software was used to identify somatic mutations in matched tumor and normal samples.

Statistical analysis

OS, RFS, and median follow-up are reported using the Kaplan–Meier and reverse Kaplan–Meier methods, respectively. Comparisons were made using the Cox proportional hazards regression model. Proportions are reported with exact 95% binomial confidence intervals (95% CI). Binomial probabilities are compared with Fisher's exact tests and reported with exact binomial 95% CIs. All P values reported are two-sided. Statistical analyses were performed using R version 4.1.0.

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Pathological, clinical, and safety outcomes

Twenty-one eligible patients were enrolled and planned for resection after receiving neoadjuvant nivolumab (**Table 1**), with one patient subsequently deemed inoperable. For the 20 patients who underwent definitive resection, data are reported here. With a median follow-up of 63 months, 5-year RFS and OS rates were 60% and 80%, respectively (**Fig. 1A** and **B**). The one patient deemed inoperable did not undergo resection due to primary progression of their disease and subsequently passed away from their cancer within 9 months of study enrollment.

As previously reported (6), rates of MPR and pCR were 45% and 10%, respectively. At 5-year follow-up, 8/9 (89%) patients with an MPR were alive and cancer-free. There was one death at 2 months in a patient with MPR without cancer recurrence, secondary to a traumatic head injury.

Six patients received standard-of-care adjuvant therapy (**Table 1**), as allowed per study protocol. Adjuvant therapy consisted of three to four cycles of cisplatin-based chemotherapy. Neither post-operative radiotherapy or targeted therapy was used as part of adjuvant treatment for this cohort.

Neoadjuvant nivolumab was associated with few side effects and did not lead to surgical delays, as had previously been reported (6). One late-onset grade 3 dermatologic immune-related adverse event (irAE) occurred 16 months after the patient's last dose of nivolumab. This event consisted of dermatitis herpetiformis with accompanying alopecia universalis, and was successfully managed with immunosuppression. No other late-onset irAEs have occurred.
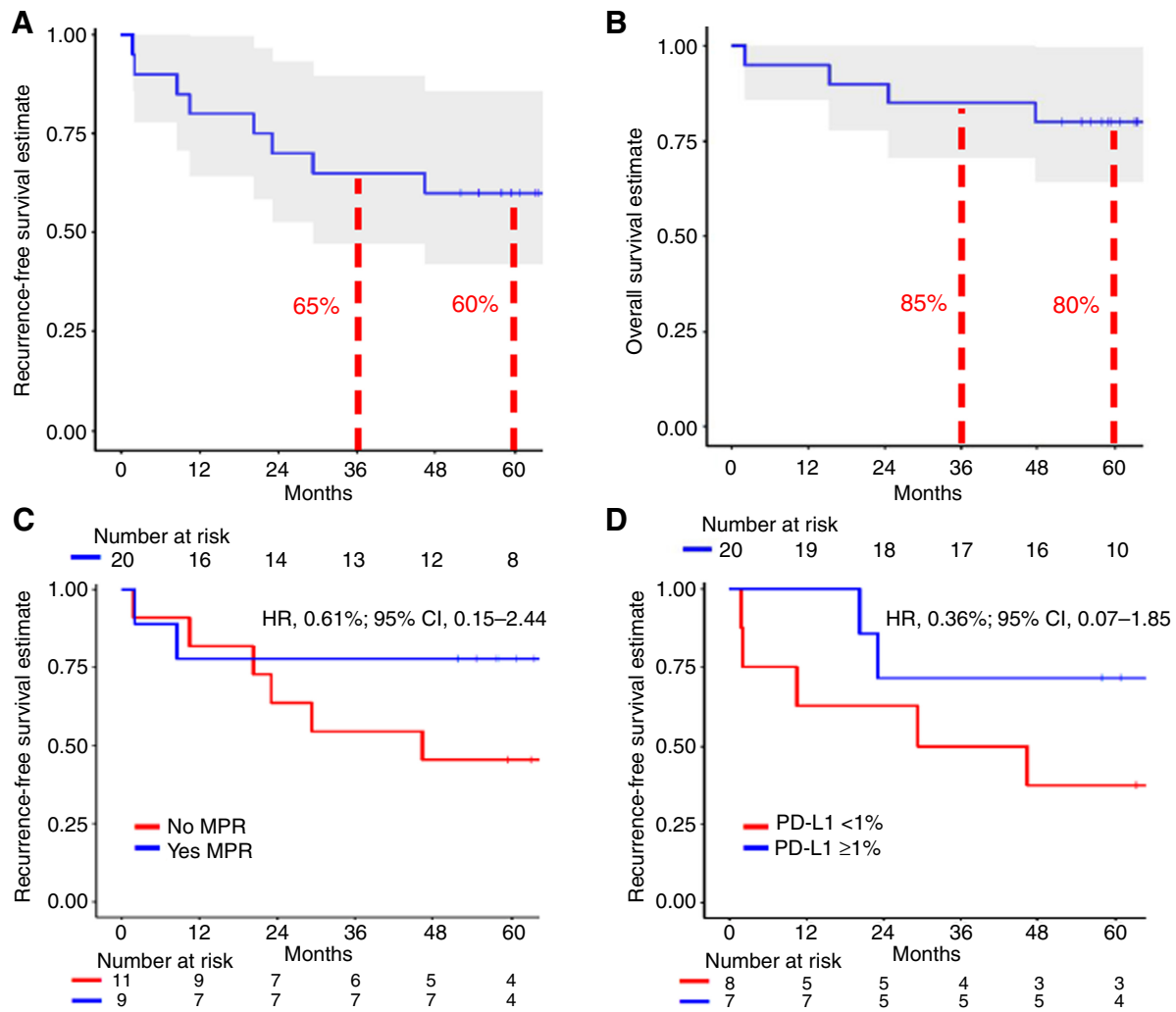
Figure 1.
A–D, Kaplan–Meier curves depicting the recurrence-free survival (**A**) and overall survival (**B**) for patients who underwent definitive resection after receiving neoadjuvant nivolumab. **C,** Depicts the recurrence-free survival for patients with or without major pathological response after neoadjuvant nivolumab. **D,** Shows the recurrence-free survival stratified by pre-treatment tumor PD-L1 expression. The dashed lines represent the 95% confidence intervals for each KM-curve. Abbreviations: Major pathological response, MPR; Programmed death-ligand 1, PD-L1; Hazard ratio, HR; Confidence Interval, CI.

Clinicopathologic subgroup analysis

At the time of analysis, the hazard ratio (HR) for presence of MPR was in the direction of improved RFS (HR, 0.61; 95% CI, 0.15–2.44; **Fig. 1C**). Pre-treatment tumor PD-L1 positivity (TPS ≥1%) trended toward improved RFS (HR, 0.36; 95% CI, 0.07–1.85; **Fig. 1D**). **Figure 2** illustrates recurrence and survival events between patients with or without MPR. The majority of recurrences, 6/7 (86%), occurred in patients without an MPR after neoadjuvant therapy. Among 6 patients with recurrence and available pre-treatment tumor PD-L1 assessment, 4 had PD-L1–negative disease (Supplementary Fig. S1). For the two patients with pCR, both remain alive and disease-free at five-year follow-up.

Patients with stage I/II disease had numerically favorable RFS compared with those with stage IIIA disease (HR, 0.42; 95% CI, 0.11–1.62; Supplementary Fig. S2A). To evaluate associations between degree of pathologic response and long-term clinical outcomes, we used an alternative cutoff value of 50% RVT, also referred

to as partial pathologic response (10, 11), which showed a favorable association with RFS (HR, 0.36; 95% CI, 0.09–1.51; Supplementary Fig. S2B). Assessed as a continuous variable, increasing %RVT trended toward increasing risk for recurrence (HR, 2.9; 95% CI, 0.51–16.57).

Examining mean TMB, when assessed as a continuous variable, was not associated with improved RFS or OS (HR, 1.0; 95% CI, 0.99–1.01; HR, 1.01; 95% CI, 1.00–1.02, respectively).

Patterns of recurrence

In total, there were seven tumor recurrences within the observation period (**Table 2**). Four recurrence events (57%) occurred greater than 1 year after surgery. Intrathoracic recurrences occurred in 3/7 (43%) patients. Among these seven patients, four remain alive after treatment for NSCLC recurrence, among whom three received successful definitive local treatment for metachronous oligometastatic disease.
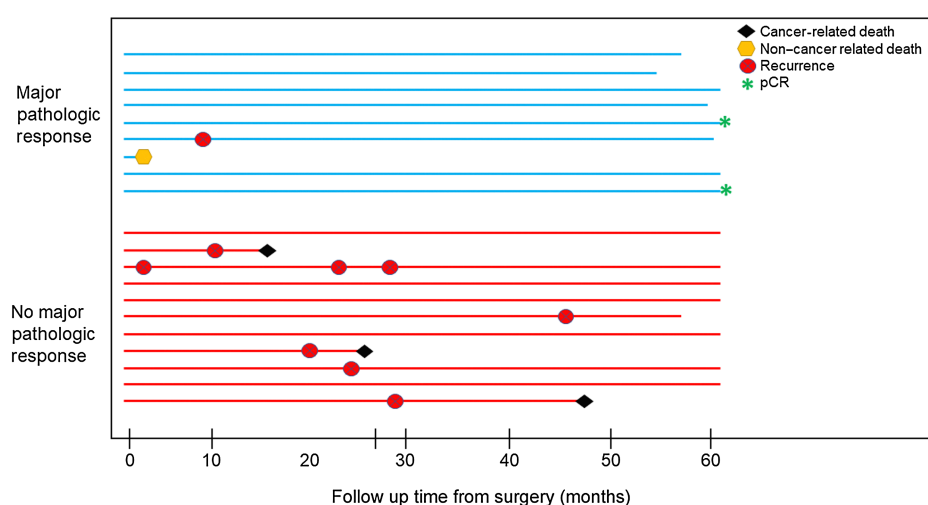
Figure 2.
Swimmer plot summarizing follow-up and recurrence patterns for patients with or without a major pathological response after neoadjuvant nivolumab. Follow-up is limited to 60 months. Abbreviation: Pathological complete response, pCR.

Discussion

Safety, feasibility, and promising clinical data from neoadjuvant PD-1 pathway blockade have prompted a proliferation of treatment strategies incorporating ICB for resectable NSCLC. In 2022, the FDA-approved neoadjuvant nivolumab plus platinum-doublet chemotherapy for stage I–IIIA NSCLC, based on results from the CheckMate-816 phase III clinical trial (5). Additional studies are testing novel immunotherapeutic combinations (12). Given the paucity of long-term data, reports such as ours, detailing 5-year clinical outcomes from the earliest reported study of neoadjuvant nivolumab, provide key insights for patients and providers.

Neoadjuvant nivolumab led to favorable clinical outcomes, with a 5-year OS rate of 80%. With the caveat of small patient numbers, this highlights potential durable benefits of ICB, even when administered briefly before surgery. Additional long-term follow-up reports, studying neoadjuvant single-agent ICB, have shown similar favorable clinical outcomes, with three-year survival rates ranging from 80% to 88.5% (13, 14). Among patients who experienced disease recurrence, several were able to receive definitive local therapy leading to extended survival.

There was a notable difference in recurrence rate based on MPR (Supplementary Fig. S1), which corresponded with a trend in improved RFS (**Fig. 1C**). Of patients with MPR, there was one

recurrence, compared with six recurrences among patients without MPR (**Fig. 2**). In addition, the two patients with a pCR remain alive and recurrence-free at 5-year follow-up. Indeed, differences in RFS based on MPR status, may in part be driven by the two patients with pCR who are included under this category. Available data from CheckMate-816 suggest that both pathological response thresholds may carry prognostic value (15), albeit questions still remain as to how this may translate into clinical decision making.

As an exploratory analysis, we evaluated an alternative pathological response threshold of 50% RVT that, in addition to MPR, showed a favorable association with RFS (Supplementary Fig. S2B), suggesting that cutoff points for pathological response beyond pCR and MPR may be worth further investigation (15). In planning future trials, prognostic markers, including pathological response or ctDNA clearance, will be critical in tailoring peri-operative management (16). Post-treatment ctDNA clearance has shown early promise as a biomarker of event-free survival (EFS) after neoadjuvant chemoimmunotherapy (17); however, conclusive interpretation may be limited by proportion of patients with available samples. How pre-surgical ctDNA clearance compares as a biomarker with post-surgical ctDNA negativity, also referred to as minimal residual disease, remains an active question (18). In addition, identifying optimal treatment strategies for patients with suboptimal pathological response—whether it be

Table 2. Summary of clinicopathologic features of 7 NSCLC recurrences among 20 patients treated with neoadjuvant nivolumab and surgical resection.

AJCC stage	Histology	PD-L1 (%)[a]	Notable Mutations	%RVT	Adjuvant chemotherapy (Y/N)	RFS duration (mo)	Intrathoracic vs. Distant Recurrence (IT/D)	Additional Treatment	Alive (Y/N)
IA	Adenocarcinoma	0	—	100	N	46.5	IT	SBRT	Y
IIA	Adenocarcinoma	0	Kras G12c, STK11	75	Y	1.8	D	Resection + SRS	Y
IIB	Adenocarcinoma	0	F11R-NRG1 fusion	100	N	29.3	IT	Carboplatin-pemetrexed	N
IIIA	Adenocarcinoma	N/A	—	5	N	8.5	IT	ChemoRT	Y
IIIA	Adenocarcinoma	60	Ros1	95	N	23.1	D	Crizotinib/ lorlatinib	Y
IIIA	Squamous	0	TP53	80	N	10.4	D	Palliative XRT	N
IIIA	Squamous	25	—	30	N	20.3	D	Unknown	N

Abbreviations: AJCC, American Joint Committee on Cancer; D, Distant; L, Local; N, No; PD-L1, Programmed death-ligand 1; %RVT, Percentage of residual viable tumor; RFS, Recurrence-free survival; Squamous, Squamous cell carcinoma; SBRT, Stereotactic Body Radiotherapy; SRS, Stereotactic radiosurgery; XRT, Radiotherapy; Y, Yes.
[a]The percentage of tumor cells expressing cell surface programmed death-ligand 1 (PD-L1) from pre-treatment biopsy specimen.

adjuvant chemotherapy or extended ICB—remains an outstanding question.

In our trial, patients with PD-L1–positive tumors trended toward improved RFS (**Fig. 1D**). This is in contrast with the initial report (6), which noted a limited correlation between pathological response and pre-treatment PD-L1 status. This may be in part due to small cohort size, with pre-treatment PD-L1 assessment available for only 15 of the 20 patients. A larger prospective trial, evaluating neoadjuvant atezolizumab, did indicate a correlation between baseline PD-L1 level and MPR, particularly for patients with TPS ≥50% (14). Subsequent studies, incorporating neoadjuvant dual-ICB and chemoimmunotherapy have shown improvement in pathological response based on pretreatment PD-L1 positivity (5, 19, 20). Specifically, results from CheckMate-816 (5), showed a significant association between PD-L1 positivity and both pathological response and EFS benefit from chemoimmunotherapy.

Although the original report of this cohort noted TMB to be predictive of pathological response to neoadjuvant nivolumab, this biomarker was not associated with improved RFS or OS. This finding is limited by availability of sequencing data, which was available for only 11 patients in our cohort. This is in contrast with a recent study evaluating neoadjuvant sintilimab (13), which noted improved disease-free survival for patients with "high" TMB. Indeed, there has been conflicting data regarding the role of TMB as a biomarker in predicting response to ICB in the metastatic setting (21–23). These conflicting findings may be in part due to variability among blood versus tissue-based assessments, sequencing platforms and established cutoff values (24). Further evaluation of TMB, in both the neoadjuvant and metastatic setting, is needed to assess its role as a predictive biomarker, either alone or integrated with additional histologic or immunologic markers (25).

As noted in our results, patients with stage I/II disease had favorable recurrence outcomes compared with those with IIIA disease after neoadjuvant ICB (Supplementary Fig. S2A). However, this may just represent the superior outcomes of a lower-risk group of patients and should be interpreted cautiously. In comparison, patients with IIIA disease treated on CheckMate-816, exhibited improved EFS with chemoimmunotherapy compared with chemotherapy alone (5). Although chemotherapy plus nivolumab will increasingly be used for resectable NSCLC, there may still be a future role for ICB-only strategies, perhaps in PD-L1 high tumors or lower-risk (I/II) disease. Identifying patients who may derive equivalent benefit from ICB alone versus chemoimmunotherapy, by incorporating predictive biomarkers, is an important goal in early- and late-stage cancers.

This study has limitations that affect our ability to draw definitive conclusions. The small cohort size makes it difficult to assign significance between histopathologic subgroups and long-term clinical outcomes. Analysis from ongoing, larger-scale trials will be needed to definitively answer the pertinent questions raised in this report.

In conclusion, neoadjuvant nivolumab monotherapy in NSCLC led to favorable long-term clinical outcomes, with a low rate of toxicity. Clinicians should be confident in using ICB in the pre-operative setting. Further long-term data evaluating the role of neoadjuvant single- and dual-agent ICB and neoadjuvant chemoimmunotherapy are awaited.

Authors' Disclosures

Authors' Contributions

S. Rosner: Conceptualization, data curation, formal analysis, investigation, visualization, methodology, writing–original draft, project administration, writing–review and editing. **J.E. Reuss:** Conceptualization, data curation, formal analysis, supervision, funding acquisition, investigation, methodology, writing–original draft. **M. Zahurak:** Software, formal analysis, validation, visualization, methodology, writing–original draft, writing–review and editing. **J. Zhang:** Software, formal analysis. **Z. Zeng:** Software, formal analysis. **J. Taube:** Resources, software, supervision, funding acquisition, investigation, methodology. **V. Anagnostou:** Conceptualization, resources, software, formal analysis, supervision, funding acquisition, validation, methodology. **K.N. Smith:** Conceptualization, resources, software, formal analysis, supervision, funding acquisition, validation, methodology. **J. Riemer:** Investigation, project administration. **P.B. Illei:** Supervision, investigation. **S.R. Broderick:** Conceptualization, investigation. **D.R. Jones:** Conceptualization, investigation. **S.L. Topalian:** Conceptualization, supervision, writing–original draft. **D.M. Pardoll:** Conceptualization, resources, formal analysis, supervision, funding acquisition, methodology. **J.R. Brahmer:** Conceptualization, supervision, investigation. **J.E. Chaft:** Conceptualization, resources, data curation, formal analysis, supervision, funding acquisition, investigation, writing–original draft, project administration. **P.M. Forde:** Conceptualization, resources, data curation, supervision, funding acquisition,

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Note

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