Tumor Response Dynamics of Advanced Non–small cell Lung Cancer Patients Treated with PD-1 Inhibitors: Imaging Markers for Treatment Outcome

Mizuki Nishino1, Suzanne E. Dahlberg2, Anika E. Adeni3, Christine A. Lydon3, Hiroto Hatabu1, Pasi A. Jänne5, F. Stephen Hodi3, and Mark M. Awad3

Abstract

Purpose: We evaluated tumor burden dynamics in patients with advanced non–small cell lung cancer (NSCLC) treated with commercial PD-1 inhibitors to identify imaging markers associated with improved overall survival (OS).

Experimental Design: The study included 160 patients with advanced NSCLC treated with commercial nivolumab or pembrolizumab monotherapy as a part of clinical care. Tumor burden dynamics were studied for the association with OS.

Results: Tumor burden change at best overall response (BOR) ranged from −100% to +278% (median, +3.5%). Response rate (RR) was 18% (29/160). Current and former smokers had a higher RR than never smokers (P = 0.04). Durable disease control for at least 6 months was noted in 26 patients (16%), which included 10 patients with stable disease as BOR. Using a landmark analysis, patients with <20% tumor burden increase from baseline within 8 weeks of therapy had longer OS than patients with ≥20% increase (median OS, 12.4 vs. 4.6 months, P < 0.001). Patients with <20% tumor burden increase throughout therapy had significantly reduced hazards of death (HR, 0.24; Cox P < 0.0001) after adjusting for smoking (HR, 0.86; P = 0.61) and baseline tumor burden (HR, 1.55; P = 0.062), even though some patients met criteria for RECIST progression while on therapy. One patient (0.6%) had atypical response pattern consistent with pseudoprogression.

Conclusions: Objective response or durable disease control was noted in 24% of patients with advanced NSCLC treated with commercial PD-1 inhibitors. A tumor burden increase of <20% from baseline during therapy was associated with longer OS, proposing a practical marker of treatment benefit. Pseudoprogression is rare in NSCLCs treated with PD-1 inhibitors. Chn Cancer Res 1–8. ©2017 AACR.

Introduction

Immune-checkpoint inhibition using programmed cell death-1 (PD-1) and programmed cell death ligand-1 (PD-L1) inhibitors has improved survival among patients with advanced non–small cell lung cancer (NSCLC; refs. 1–7). With the approval of pembrolizumab, nivolumab, and atezolizumab for NSCLCs previously treated with platinum doublet chemotherapy and the approval of pembrolizumab in the first-line setting for NSCLCs with ≥50% PD-L1 expression, almost every patient with advanced NSCLC will be exposed to immune-checkpoint inhibitor therapy at some point over the course of treatment. In addition, the recent approval of pembrolizumab with carboplatin and pemetrexed as a first-line therapy for metastatic nonsquamous NSCLC regardless of PD-L1 expression levels further expands the usage of immune-checkpoint inhibitor therapy for treatment of advanced NSCLC (8).

Distinct immune-related response patterns of tumor burden dynamics have been described on serial CT scans performed for treatment monitoring of patients treated with immune-checkpoint inhibitors, including cytotoxic T-lymphocyte antigen-4 (CTLA-4) inhibitors and PD-1/PD-L1 inhibitors (9–12). Patients treated with these agents may demonstrate an initial tumor burden decrease, either by growth of existing lesions or the appearance of new lesions, followed by a subsequent decrease of tumor burden (9–14). This response pattern, termed pseudoprogression, poses a challenge in clinical decision making and is thus recognized as an area in need of further investigation among the immuno-oncology community (9, 13, 15, 16). The reported incidence of pseudoprogression is 10% or less in patients with melanoma treated with immune-checkpoint inhibitors (9, 10, 14), and 4.6% in patients with NSCLC (6/129) treated with nivolumab (2). However, there are limited data on the incidence and detailed characteristics of pseudoprogression among patients with NSCLC, especially among those who are treated with commercial PD-1 inhibitors.

In addition, in most of the clinical trial settings, patients who experienced an initial response to therapy and then met with...
Immune-checkpoint inhibition targeting the PD-1/PD-L1 pathway has become a major therapeutic option for patients with advanced non–small cell lung cancer (NSCLC). Unique immune-related tumor burden dynamics have been reported, providing challenges in clinical decision making, such as whether to continue treatment beyond initial tumor progression. In the current study of 160 patients with advanced NSCLC treated with commercial PD-1 inhibitors, a significant overall survival benefit was found in patients whose tumor burden did not increase by 20% or more compared with baseline, even though some patients who initially responded have met criteria for RECIST progression during therapy. The observation proposes a practical objective marker of treatment benefit of PD-1 inhibitor therapy that is distinct from RECIST-based progression. Pseudoprogression was exceedingly rare and was noted in only one patient (0.6%). The study provides valuable observations that can be validated in larger cohorts of patients with NSCLC to optimize treatment with immune-checkpoint inhibitors.

### Materials and Methods

#### Patients

The study population included 160 patients with advanced NSCLC treated with commercial nivolumab or pembrolizumab monotherapy at Dana-Farber Cancer Institute (Boston, MA) as a part of routine clinical care after its FDA approval between March 2015 and August 2016. All patients had baseline CT scans prior to the initiation of therapy demonstrating at least one measurable lesion and had at least one follow-up CT scan during therapy available for review. Initial tumor responses in 56 of the 160 included patients with NSCLC have been reported previously (24). The medical records and imaging studies of these patients were retrospectively reviewed with the approval of the Dana Farber/ Harvard Cancer Center Institutional Review Board. The study was in compliance with Health Insurance Portability and Accountability Act, and all patients provided written informed consent.

### Tumor measurements on the longitudinal scans

Baseline and all follow-up CT scans during therapy were retrospectively reviewed by a board-certified radiologist (M. Nishino) to quantify tumor burden changes using immune-related RECIST (irRECIST), based on previously published studies (12, 20, 21, 24). Unidimensional, RECIST-defined measurements were used in irRECIST because they have been shown to have higher reproducibility compared with bidimensional measurements used in WHO criteria and irRC, and are in alignment with the RECIST-based assessments used in most of the solid tumor trials performed in the past decade (15, 16, 21, 25–27). In brief, target lesions (≥10 mm in the longest diameter for nonnodal lesions and ≥15 mm in short axis for nodal lesions) were selected on baseline scans, allowing up to two lesions per organ and up to five lesions in total as in RECIST1.1 (18, 24, 28, 29). Measurements of target lesions were performed on baseline and all follow-up CT scans throughout therapy. If new lesions were noted on the follow-up scans, the measurements of the new lesions were included in the sum of the measurements (11, 14, 20, 21). Up to two per organ and five in total new lesions were allowed at each time point (14, 20). New lesions had to be ≥10 mm in the longest diameter for nonnodal lesions and ≥15 mm in short axis for nodes to be included in the measurements (20). Other imaging studies, such as brain MRI and PET/CT scans, were also reviewed to identify new lesions and assess nontarget lesions, as described previously (30). Follow-up scans were performed per treating providers’ discretion without predefined intervals in these patients treated as a part of routine clinical care. One observer performed the serial measurements for all patients, because the previous study has demonstrated high interobserver agreements of the measurements using this method (21).

### Assessment of tumor response and progression

Immune-related best overall response (irOR) during therapy was assigned to each patient per irRECIST as in the prior studies (12, 20, 21, 24). Confirmation on two consecutive scans at least 4 weeks apart was required for irPD (11, 14, 20, 21, 24). Time to progression using irRECIST (irTTP) was obtained in each patient, allowing the inclusion of new lesion measurements and requiring confirmation of PD (20, 21). TTP according to conventional RECIST1.1 was also obtained in each patient, where appearance of new lesions or tumor burden increase ≥20% and 5 mm comparing with the nadir immediately defined PD without requiring confirmation. Spider plots of the tumor burden changes throughout therapy for all patients were generated to visually demonstrate tumor burden dynamics during therapy.

### Statistical analysis

Comparison across groups was performed using a Fisher exact test for categorical variables and a Kruskal–Wallis test for continuous variables. TTP by RECIST1.1 and irTTP were estimated using the method of Kaplan–Meier. The 8-week conditional landmark analyses were performed to assess relationships between OS and tumor burden dynamics during the first 8 weeks of therapy. Extended Cox models with time-dependent covariates were used to evaluate associations between OS and tumor burden dynamics throughout therapy. Multivariable Cox models were used to adjust for clinical variables and potential confounders. All P values are based on a two-sided hypothesis. A P value of less than 0.05 was considered to be significant.

### Translational Relevance

**Immune-checkpoint inhibition targeting the PD-1/PD-L1 pathway has become a major therapeutic option for patients with advanced non–small cell lung cancer (NSCLC). Unique immune-related tumor burden dynamics have been reported, providing challenges in clinical decision making, such as whether to continue treatment beyond initial tumor progression. In the current study of 160 patients with advanced NSCLC treated with commercial PD-1 inhibitors, a significant overall survival benefit was found in patients whose tumor burden did not increase by 20% or more compared with baseline, even though some patients who initially responded have met criteria for RECIST progression during therapy. The observation proposes a practical objective marker of treatment benefit of PD-1 inhibitor therapy that is distinct from RECIST-based progression. Pseudoprogression was exceedingly rare and was noted in only one patient (0.6%). The study provides valuable observations that can be validated in larger cohorts of patients with NSCLC to optimize treatment with immune-checkpoint inhibitors.**
Results

Immune-related response and tumor burden dynamics

The clinicopathologic characteristics of 160 patients with advanced NSCLC are shown in Table 1. Of the 160, 140 patients were treated with nivolumab, and 20 patients were treated with pembrolizumab. The median follow-up for this population was 9.7 months. Tumor burden change in reference to baseline at irBOR ranged from $-100\%$ to $+278\%$ (median, $+3.5\%$; Fig. 1).

Response rate by irBOR throughout therapy was 18% [29/160; immune-related partial response (irPR) in 29]. Current and former smokers had higher response rates than never smokers (response rate: 14% (8/58), 25% (20/79), 4% (1/23), respectively; Fisher $P = 0.04$). Durable disease control, defined as tumor burden below 20% increase from baseline for at least 6 months, was noted in 26 patients (16%); among these 26 patients, irBOR was irPR in 16 patients and was immune-related stable disease (irSD) in 10 patients. Median TTP by irRECIST was 11.4 months [95% confidence interval (CI) for the median, 11.3–11.4] and was 3.7 months (95% CI for the median, 2.1–5.7) by conventional RECIST1.1.

The spider plots demonstrate tumor burden dynamics during PD-1 inhibitor therapy of the cohort (Fig. 2). In 87 patients (54%), tumor burden stayed below 20% increase of baseline throughout therapy (Fig. 2). Of note, among these 87 patients, 14 patients (16%) have met the criteria for PD by conventional RECIST during PD-1 therapy, and four of them (5%) even had confirmed irPD by irRECIST; however, these 18 patients continued on treatment with immunotherapy and experience an ongoing clinical benefit. In the remaining 73 patients (46%), tumor burden increased $\geq 20\%$ of baseline burden at some time point during therapy; among these patients, one patient experienced subsequent tumor burden decrease, demonstrating an atypical response pattern (Fig. 2, arrow), discussed further below. On the basis of the observations of the spider plot, a $\geq 20\%$ increase in tumor burden from baseline was applied as a threshold to study its relationship with OS benefit.

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*Includes poorly differentiated NSCLC or NSCLC not otherwise specified ($n=12$) and large cell carcinoma or NSCLC with neuroendocrine features ($n=8$).
Relationships between overall survival and tumor burden dynamics

A total of 76 deaths were observed among 160 patients at the time of data analyses. Overall survival (OS) was compared between subgroups defined by the threshold of ≥20% increase in tumor burden from baseline, using an 8-week landmark analysis and extended Cox models. The 8-week landmark time point was chosen because it was the median time to reaching ≥20% threshold among those who experienced tumor burden increase ≥20% from baseline. In addition, an 8-week time point has been previously studied to identify early markers for outcome in patients with advanced NSCLC (31–33).

After excluding patients with survival time shorter than that landmark time point of 8 weeks, a total of 143 patients were studied in the landmark analysis. Among them, 104 patients with <20% tumor burden increase compared with the baseline burden within 8 weeks of therapy had longer OS compared with 39 patients who experienced ≥20% increase by 8 weeks (median OS: 12.4 vs. 4.6 months, log-rank P < 0.001; Fig. 3). In the multivariable analysis, these 104 patients had significantly reduced hazards of death (HR, 0.24; P < 0.0001) after adjusting for smoking (HR, 0.85; P = 0.62) and loge (baseline tumor burden) greater than the median (HR, 1.63; P = 0.056).

The extended Cox models with time-dependent covariates included all 160 patients who were initially classified as having tumor burden increase <20% from baseline. Any patient who experienced ≥20% increase from baseline was reclassified into the other group at that time during therapy. Patients whose tumor burden stayed below 20% increase from baseline throughout therapy had significantly reduced hazards of death compared with those who experienced tumor burden increase ≥20% from baseline burden at any time point during therapy (HR, 0.24; P < 0.0001), after adjusting for smoking comparing never smoker versus current/former smoker (HR, 0.86; P = 0.61) and loge (baseline tumor burden) greater than the median (HR, 1.55; P = 0.062).

Atypical response pattern

One patient (0.6%) had atypical response pattern or "pseudo-progression," where tumor burden initially increased beyond ≥20% meeting the criteria for progression and subsequently decreased to the range of stable disease (Fig. 4). The patient experienced tumor burden increase and subsequent regression, without new lesions. Progression was confirmed on three consecutive scans performed over 5 months since the initial scan demonstrating PD, fulfilling the criteria for irPD, before tumor regression to the baseline burden (+0%) was noted at 8.8 months of therapy.

Figure 2.
Spider plot of tumor burden changes during PD-1 inhibitor therapy. Tumor burden stayed below 20% increase compared with baseline throughout therapy in 87 patients (54%; lines below the dotted horizontal line). Among the remaining 73 patients (46%) who experienced tumor burden increase ≥20% at some time point during therapy, one patient experienced tumor burden decrease after initial increase, demonstrating an atypical response pattern (purple line indicated by an arrow).

Figure 3.
Kaplan-Meier estimates of OS of patients dichotomized by tumor burden changes at the 8-week landmark time point. Patients with <20% tumor burden increase compared with the baseline within 8 weeks of therapy had longer OS compared with those who experienced ≥20% increase by 8 weeks (median OS, 12.4 vs. 4.6 months; log-rank P < 0.001).
the current observation (4, 7), although it remains to be tested with stratification by PD-L1 status. Other demographics and clinical characteristics were not associated with response to PD-1 inhibitors. PD-L1 IHC staining of tumor specimens was not consistently available in these commercially treated patients, because this biomarker was not required to prescribe the PD-1 inhibitor in this population of previously treated NSCLC patients. Because durable "stable disease" is described as one of the response patterns in patients treated with immune-checkpoint inhibitors, we also investigated the number of patients with durable disease control, defined as tumor burden below 20% increase from baseline for at least 6 months, which was noted in 26 patients (16%), including 10 patients with irSD as their irBOR. Therefore, this assessment of durable tumor burden control identified additional 10 patients with potential treatment benefits that may not be recognized by response rate evaluations alone. Together with those who achieved irPR, a total of 39 patients (24%) of the cohort demonstrated objective findings on serial CT scans, indicative of treatment benefit. Median TTP was 3.7 months by RECIST1.1, which is in agreement with the median PFS of 1.9 to 3.7 months reported in the trials using RECIST1.1 (1–4). Median TTP by irRECIST was longer at 11.4 months, which was expected because of the modified definition of PD by irRECIST that requires confirmation and allows new lesions in the measurements (20, 21, 24).

The spider plot of tumor burden dynamics on serial scans provides further information of the immune-related response patterns in the cohort. In 54% of the patients, tumor burden stayed below 20% increase of baseline throughout therapy, which was noted with prolonged therapy duration and survival. On the basis of the observation of the spider plot, the association between OS and tumor burden increase <20% from baseline was studied using the 8-week landmark analysis and the Cox proportional hazards models with a time-varying covariate. In both methods, the tumor burden increase <20% from baseline was significantly
associated with longer OS, which remained significant after adjusting for other factors, including smoking and baseline tumor burden. These results provide a practical marker for survival and treatment benefit during PD-1 inhibitor therapy for patients with advanced NSCLC, which can be further studied in a larger prospective cohort to objectively guide clinical decisions.

The threshold of <20% increase from baseline has also been identified as a potential marker for prolonged OS in melanoma patients treated with pembrolizumab in a recent study (10). Of note, the 20% increase from baseline corresponds to the criteria for RECIST-PD only in patients who do not experience tumor decrease during therapy. Patients who experience initial tumor decrease may meet criteria for RECIST-PD even though their tumor burden is well below the baseline burden, because RECIST compares the tumor burden with the nadir (the smallest burden since baseline during therapy) to define progression after initial response (17, 18). Indeed, 16% of the patients (14/87) with tumor burden increase <20% throughout therapy met criteria for RECIST-PD during therapy, in spite of OS benefits of the group demonstrated by the survival analyses, further emphasizing that the 20% threshold from the baseline rather than the nadir is a marker that is distinct from RECIST-based progression. Moreover, the 20% change of tumor burden has been shown to be confidently identified as true tumor change, because it is outside of the measurement errors based on the 95% limits of interobserver agreements in the prior report of measurement variability of immune-related response evaluations (21).

In addition to the group with durable treatment benefit, the serial analysis of tumor burden dynamics also helps to identify the spectrum of progression at the early course of therapy. A subset of cases among those with marked increase of tumor burden by 8 weeks may be attributed to “hyperprogression,” which is a newly reported pattern of progression during PD-1/PD-L1 inhibitor therapy can be additional focus in future studies (34).

Pseudoprogression was noted in one of 160 patients (0.6%) in the cohort, indicating that this is a very rare phenomenon among patients with advanced NSCLC treated with commercial PD-1 inhibitors. Notably, irPD was confirmed on two or more consecutive scans over the period of 5 months in this patient, before experiencing tumor burden reduction. Similar observations have been described in patients with melanoma treated with pembrolizumab (10), and together with the current results, the limitations of current strategy of immune-related response evaluations were clearly demonstrated. Specifically, there is a need for scientific evidence to optimize the minimum time frame required for confirming PD (10, 22). In light of the rarity of pseudoprogression in NSCLC, treatment with PD-1 inhibitors should likely be discontinued in most patients with clear radiographic disease progression, especially in the setting of clinical deterioration.

The limitation of the current study includes a retrospective design with patients treated at a single institution, and the candidate radiographic marker for survival benefit that we identified should ideally be validated in larger, prospective multi-institutional cohorts. The initial tumor responses to nivolumab among 56 of the 160 patients have been previously reported (24); however, the previous study had a much shorter follow-up time (median, 3.8 months) and focused on initial tumor responses and did not include survival analyses. Moreover, the cohort size has been nearly tripled as the prior study with a much longer follow-up time (median, 9.7 months), and both nivolumab- and pembrolizumab-treated patients are included. Therefore, the current study provides new information in every aspect of the study, including tumor response durability, survival analyses, and pseudoprogression. Assessment of PD-L1 immunostaining and other biomarkers, such as tumor mutation burden, was not consistently available in this commercially treated cohort; however, these biomarkers are under active investigation in prospective trials of immune-checkpoint inhibitors.

The current assessment of irRECIST uses diameters as a simple and practical measure and does not include tumor volumes. As tumor volume has also been shown to be a reproducible marker to characterize tumor response and progression and predict survival for advanced NSCLC treated with molecular targeted therapy including EGFR inhibitors (33, 35, 36), the utility of tumor volume in the setting of immune-related response evaluations can be tested in future studies. The response assessment of irRECIST is based on the sum of the target lesion measurements in each patient and does not reflect different behaviors of individual lesions in one patient. Heterogeneous response patterns of individual lesions in one patient, which are often anecdotally called “mixed responses,” may also be further investigated in the cohorts treated with immune-checkpoint inhibitors.

The observations in the current study also need to be further studied in the first-line setting, as the patients in the current study have been previously treated prior to receiving commercial PD-1 inhibitors. The major goal of the current study was to describe the detailed tumor burden characteristics of patients treated with commercial agents in a more practical environment outside the setting of a clinical trial and provide a potential marker of clinical outcome for further investigation to better guide treatment decisions by oncologists.

In conclusion, an objective response or durable tumor burden control was noted in 24% of the patients treated with commercial PD-1 inhibitors in the clinical setting. Tumor burden increase of less than 20% from baseline was associated with longer OS, proposing a practical marker for prolonged survival and treatment benefits that is distinct from RECIST-based response or progression, which can be further studied in larger prospective cohorts of patients with advanced NSCLC. Pseudoprogression was exceedingly rare and was noted in only 0.6% of the population.

Disclosure of Potential Conflicts of Interest
M. Nishino reports receiving commercial research grants from Merck and Toshiba Medical Systems, speakers bureau honoraria from Bayer, and is a consultant/advisory board member for Bristol-Myers Squibb, Toshiba Medical Systems, and WorldCare Clinical. S.E. Dahlberg is a consultant/advisory board member for AstraZeneca. H. Hatabu reports receiving commercial research grants from and is a consultant/advisory board member for Toshiba Medical Systems. P.A. Janne reports receiving commercial research grants from AstraZeneca, Daiichi Sankyo, Eli-Lilly, and PUMA, holds ownership interest (including patents) in Gatekeeper Pharmaceuticals, and is a consultant/advisory board member for ARIAD, AstraZeneca, Boehringer Ingelheim, Chugai Pharmaceuticals, Eli Ljilj, Genentech/Roche, Ignyta, LOXO Oncology, Merrimack Pharmaceuticals, and Pfizer. F.S. Hodi reports receiving commercial research grants from Bristol-Myers Squibb and is a consultant/advisory board member for Amgen, Bristol-Myers Squibb, EMD Serono, Genentech, Merck, and Novartis. No potential conflicts of interest were disclosed by the other authors.

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Nishino, A.E. Adeni, P.A. Janne, F.S. Hodi, M.M. Awad
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Nishino, S.E. Dahlberg, F.S. Hodi, M.M. Awad

Writing, review, and/or revision of the manuscript: M. Nishino, S.E. Dahlberg, A.E. Adeni, H. Hatabu, P.A. Jänne, F.S. Hodi, M.M. Awad

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References


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