Systematic evaluation of pembrolizumab dosing in patients with previously treated non-small cell lung cancer

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ABSTRACT (299 words; limit, 300 words)

Introduction: In the phase I KEYNOTE-001 study, pembrolizumab 10 mg/kg every 2 weeks (Q2W) or Q3W demonstrated durable antitumor activity in patients with previously treated advanced non-small cell lung cancer (NSCLC). We sought to characterize the relationship between pembrolizumab dose, exposure, and response in KEYNOTE-001 to define an effective dose for patients with previously treated advanced NSCLC.

Methods: Patients received pembrolizumab 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W. Response was assessed per RECIST v1.1 at weeks 9, 18, and 27. Exposure-efficacy analysis was used to characterize the relationship between pembrolizumab area under the concentration-time curve at steady-state over 6 weeks ($AUC_{ss\text{-}6wk}$) and tumor size (sum of longest diameters). Dependence of change in tumor size on pembrolizumab exposure was analyzed graphically and by nonlinear mixed effects modeling. Exposure-safety analysis was used to characterize the relationship between pembrolizumab $AUC_{ss\text{-}6wk}$ and the occurrence of adverse events of interest based on their immune etiology.

Results: No significant dose-exposure dependency in efficacy or safety was identified. Week 27 response rates in patients with tumors expressing PD-L1 in ≥1% of tumor cells were comparable between 2 mg/kg and 10 mg/kg (15.7% [95% CI, 8.1-29.0] and 19.8% [95% CI, 15.5- 25.0], respectively). Regression analyses of percent change from baseline in tumor size versus $AUC_{ss\text{-}6wk}$ indicated a flat relationship (regression slope $P > 0.05$). Model-simulated response rates normalizing for prognostic covariates (PD-L1 expression and *EGFR* mutation status) also suggest exposure-response to be flat and therefore most likely close to the 2 mg/kg Q3W efficacy plateau. The adverse event incidence is predicted to be similar among the clinically tested doses.

Conclusions: Analyses show similar efficacy and safety profiles for pembrolizumab across doses of 2 mg/kg to 10 mg/kg. These results support the use of a 2-mg/kg Q3W dosage in patients with previously treated advanced NSCLC.

ClinicalTrials.gov registry: NCT01295827

Keywords: Non-small cell lung cancer; pembrolizumab; PD-1; PD-L1; immunotherapy

INTRODUCTION

Under normal physiological conditions, immune checkpoints are inhibitory pathways critical for maintaining self-tolerance and limiting tissue damage when the immune system is responding to pathogenic stimuli [1]. Tumors frequently exploit immune checkpoint pathways such as the programmed death receptor 1 (PD-1) pathway to evade immune surveillance [1,2]. PD-1 is a negative co-stimulatory receptor expressed mainly on activated T cells, and its ligand, PD-L1, is highly expressed on the surface of cells from multiple tumor types [3,4]. Binding of PD-L1 to the PD-1 receptor enhances proliferation of regulatory T cells that suppress effector immune responses [1].

Pembrolizumab is a highly selective, humanized anti–PD-1 monoclonal antibody that has demonstrated efficacy and a manageable toxicity profile across multiple dosages in several advanced malignancies [5–12]. Currently, pembrolizumab is approved in several countries for the treatment of advanced melanoma at a dose of 2 mg/kg every 3 weeks (Q3W). Five randomized comparisons in the melanoma setting demonstrated no difference in efficacy or safety between pembrolizumab 2 mg/kg Q3W and 10 mg/kg Q3W or between 10 mg/kg Q3W and Q2W [7,8,11–13]. In a pooled analysis of 495 patients with previously treated or treatment-naive advanced non-small cell lung cancer (NSCLC) enrolled in the multicohort phase Ib KEYNOTE-001 study (ClinicalTrials.gov identifier, NCT01295827), pembrolizumab 10 mg/kg Q2W and Q3W demonstrated durable antitumor activity with a manageable toxicity profile [14]. Importantly, a clear relationship between higher tumor PD-L1 expression and improved efficacy was observed.

We present topline efficacy and safety data for a KEYNOTE-001 expansion cohort of patients with previously treated NSCLC who received pembrolizumab 2 mg/kg Q3W, as well

as analyses of the relationship between pembrolizumab exposure and tumor response and adverse events (AEs) of special interest based on their immune etiology.

METHODS

Study design

As previously described, KEYNOTE-001 was a multicenter, open-label, phase 1 trial that included multiple expansion cohorts of patients with advanced NSCLC [14]. Key eligibility criteria for the cohort reported here included age ≥18 years, locally advanced or metastatic NSCLC, disease progression following treatment with platinum-based chemotherapy and the appropriate tyrosine kinase inhibitor (if positive for a sensitizing *EGFR* mutations or *ALK* translocation), Eastern Cooperative Oncology Group performance status of 0-1, PD-L1 expression in ≥1% of tumor cells, adequate organ function, no history of pneumonitis, no systemic immunosuppressive therapy, or active autoimmune disease.

All patients provided written informed consent. The study was conducted in accordance with the protocol, good clinical practice standards, and the Declaration of Helsinki. All protocols and amendments were approved by the appropriate institutional review board or ethics committee at each participating institution.

Treatment and assessments

Pembrolizumab was administered intravenously at a dose of 2 mg/kg Q3W, 10 mg/kg Q3W, or 10 mg/kg Q2W. Patients remained on pembrolizumab until disease progression assessed per immune-related response criteria [15] by investigator review. Unacceptable toxicity led to dose delay, a prolonged dosing interval, or discontinuation; dose reduction was not allowed. Tumor imaging was performed at baseline and every 9 weeks thereafter. Response was

assessed per RECIST v1.1 by independent central review. AEs were collected throughout the study and for 30 days after treatment discontinuation (90 days for serious AEs) and graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. AEs of special interest based on immune etiology were identified from a prespecified list of terms (see supplementary table) and reported regardless of attribution to treatment by the investigator. PD-L1 expression was assessed in contemporaneous biopsy samples using immunohistochemistry and the 22C3 anti-human PD-1 antibody (Merck). For enrollment, PD-L1 expression was assessed using a prototype assay, with positivity defined as membranous staining in ≥1% of cells within tumor nests or staining in stroma. The PD-L1 proportions score (PS), was defined as the percentage of cells with membranous PD-L1 staining as assessed using a clinical trial immunohistochemistry assay [14]. Blood samples (3.5 mL) for peak and trough pharmacokinetic assessment were collected at cycles 1 and 2. After cycle 2, trough samples were collected every 12 weeks for the first 12 months and every 6 months thereafter. Pembrolizumab concentration in serum was assessed using an electrochemiluminescent assay.

Exposure-Efficacy Analysis

Full details are provided in a companion manuscript. Briefly, the pembrolizumab pharmacokinetic profile was characterized using a population modeling approach. Patients enrolled in all previously treated NSCLC cohorts of KEYNOTE-001 who had pharmacokinetic data and measurable disease per central review at baseline were included in the exposure-efficacy modeling analysis. Exposure was defined as the area under the concentration-time curve at steady state over 6 weeks ($AUC_{ss\text{-}6wk}$), estimated by the population pharmacokinetic model. Tumor size was defined as the sum of the longest diameter (SLD) of target lesions.

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An exploratory graphical analysis was performed to evaluate change in tumor size (observed SLD) at 18 weeks postbaseline versus pembrolizumab exposure. Week 18 was chosen because it was the latest common time point reached by all patients. The change in tumor size over time was formally analyzed using a nonlinear mixed effects modeling approach, incorporating first-order tumor growth and shrinkage rates and assuming that a fraction of the lesions were accessible for immune-mediated antitumor effect, with the remaining tumor portion insensitive to treatment. Population parameter values and interindividual variability were estimated from the available data. Patient- and study-specific factors such as PD-L1 expression, *EGFR* mutation status, baseline tumor size, and smoking history were explored as covariates to explain variability on model parameters. Consistent with an understanding of the pharmacology, the effect of pembrolizumab was included as an additional estimated parameter on the modeled tumor shrinkage rate.

Simulations were conducted to translate the model-estimated exposure-response relationship into SLD tumor size response at week 27, categorized into one of three response categories analogous to RECIST v1.1 criteria: progressive disease (PD; ≥20% increase in SLD from baseline), stable disease (SD: change in SLD from baseline between -30% and +20%), and response (PR; SLD reduction from baseline ≥30%). Full methodological details are described in the companion manuscript.

Exposure-Safety Relationship

Analysis of the relationship between pembrolizumab $AUC_{ss\text{-}6wk}$ and the incidence of AEs of special interest based on immune etiology was performed using nonlinear mixed effects modelling. Patients enrolled in all NSCLC cohorts of KEYNOTE-001 who had

pharmacokinetic data were included in the analysis. Logistic regression was used to analyze the frequency of AEs of special interest. To account for the significant effect of treatment duration on the occurrence of these AEs, time-to-event analysis was also performed.

RESULTS

Efficacy and Safety of Pembrolizumab 2 mg/kg Q3W

Between April 03, 2014 and July 14, 2014, 55 patients with previously treated NSCLC were enrolled and treated with pembrolizumab 2 mg/kg Q3W. Patient characteristics were as expected for a previously treated advanced NSCLC population. As of the January 23, 2015, data cutoff date, all patients had a minimum follow-up duration of 27 weeks, 15 (27.3%) patients remained on pembrolizumab, 20 (36.4%) had experienced disease progression, and 12 (21.8%) had died. ORR and the disease control rate (DCR) per RECIST v1.1 by central review were 15.4% (95% CI, 6.9%-28.1%) and 50.0% (95% CI, 35.8%-64.2%), respectively, in patients with measurable disease at baseline (n = 52). ORR (95% CI) was 30.4% (13.2%-52.9%), 0% (0.0%-14.8%), and 25.0% (0.6%-80.6%) patients with PD-L1 PS ≥50% (n = 23), 1%-49% (n = 23), and <1% (n = 4), respectively. Cumulative response and disease control rates were similar in the patients in this cohort treated at 2 mg/kg Q3W and in previously treated patients from a randomized KEYNOTE-001 cohort of pembrolizumab 10 mg/kg Q3W versus 10 mg/kg Q2W (**Table 1**).

Treatment-related AEs were reported for 26 (47.3%) patients treated with pembrolizumab 2 mg/kg Q3W. Five patients reported grade 3-5 treatment-related AEs (n = 2 grade 3 colitis and n = 1 each grade 5 cardiorespiratory arrest, grade 4 pneumonitis, and grade 3 pneumonitis). Treatment was discontinued because of drug-related AEs in 3 (5.5%) patients. AEs of special

interest based on immune etiology occurred in 8 (14.5%) patients: colitis (n = 2 grade 3, n = 1 grade 1), pneumonitis (n = 1 each grade 3 and 4), and exfoliative dermatitis (n = 1 grade 1).

Considering all 550 patients with NSCLC enrolled in KEYNOTE-001, the AE profile observed at 2 mg/kg Q3W was mostly similar to that observed in patients treated at higher dosages (**Table 2**). The somewhat lower incidence of AEs at 2 mg/kg Q3W is likely a reflection of the approximately 2-fold shorter follow-up duration in patients treated at this dose (**Table 2**).

Exposure-Efficacy Relationship

At week 18, tumor size and exposure data were available for 222 patients, of whom 170 had ≥1 previous treatment. Observed tumor size data (SLD) showed a wide range of longitudinal response patterns across the previously treated population. There was a flat relationship between exposure and tumor size reduction at 18 weeks, with overlapping CIs observed between subsets defined by binned $AUC_{ss\text{-}6wk}$ (**Figure 1**). The linear regression slope estimates were not significantly different from zero, with *P* values greater than the prespecified significance level (0.05). Similarly, there was a flat relationship between tumor size reduction and exposure, stratified by PD-L1 expression at week 18 (**Figure 2**). Linear regression slope estimates were modest and not significantly different from zero ($P > 0.05$).

In agreement with the exploratory graphical and linear regression analyses of week 18 observed data, individual pembrolizumab exposures also showed no statistically significant influence on the model-estimated tumor shrinkage rate ($P = 0.54$ based on –2 log-likelihood reduction and $\chi 2$ test). The 95% CIs of the exposure response parameter was found to overlap

with zero (range, –0.186 to 0.359), consistent with no significant difference from a flat exposure-response relationship.

Exposure-Response Simulations

Accounting for differences in tumor growth patterns associated with *EGFR* mutation and PD-L1 expression status, model-simulated median response rates at week 27 for patients with PD-L1 PS ≥50% were 38.8% (90% CI, 30.7%-46.0%) for 2 mg/kg Q3W and 43.5% (90% CI, 37.2%-49.3%) at 10 mg/kg Q2W (**Figure 3A**). The CIs for patients with PD-L1 PS 1-49% also showed overlap (**Figure 3A**).

Exposure-Safety Relationship

A total of 544 patients were evaluable for the relationship between exposure and safety. Logistic regression analysis identified treatment duration as a significant factor for occurrence of AEs of special interest based on immune etiology. After inclusion of treatment duration in the model, no significant relationship between pembrolizumab exposure and AEs of immune etiology was found ($P = 0.57$). Similarly, pembrolizumab exposure was not significantly correlated with the hazard for the occurrence of AEs of immune etiology in the time-to-event analysis ($P = 1.0$). Apart from treatment duration, none of the investigated covariates was a significant predictor of the probability of experiencing an AE of special interest. Based on simulations from the final logistic regression model, even when forcing a relationship with pembrolizumab exposure, the predicted incidence of AEs of special interest at 9 months was very similar at 2 mg/kg Q3W (26%), 10 mg/kg Q3W (27%), and 10 mg/kg Q2W (28%).

DISCUSSION

Based on the clinical efficacy and safety data and clinical pharmacology modeling and simulation reported here, the 2-mg/kg Q3W dose of pembrolizumab approved in melanoma also provides clinically significant antitumor activity in NSCLC, with an efficacy and safety profile comparable to those observed with doses of 10 mg/kg Q3W or 10 mg/kg Q2W. Given the similar efficacy and safety between the 2 mg/kg and 10 mg/kg doses, the benefit-risk profile at the higher dose level is not expected to be better than at 2 mg/kg Q3W.

The efficacy profile of the 2 mg/kg Q3W dose regimen is further supported by early translational and biomarker pharmacokinetic/pharmacodynamic results whereby potential clinical efficacy was predicted on the basis of integration of available preclinical pharmacokinetics, PD-1 receptor occupancy and anti-tumor efficacy data from a syngeneic mouse model, early clinical pharmacokinetic data, as well as human disease properties [16]. This analysis predicted 1-2 mg/kg Q3W as the lowest dose with a high likelihood of providing substantial clinical benefit in patients with NSCLC. This observation is consistent with 2 mg/kg Q3W falling near the plateau of the underlying exposure-response and achieving clinical efficacy comparable to 10 mg/kg doses.

In conclusion, we report a similar ORR regardless of dose and an overall flat relationship between exposure and tumor size across the range of 2 mg/kg Q3W to 10 mg/kg Q2W in patients with previously treated NSCLC. The lack of a clear trend in estimated effects indicates there is no significant difference in efficacy or safety among the three dose levels. Therefore, the totality of available data supports 2 mg/kg Q3W as the recommended pembrolizumab dosing regimen in patients with NSCLC.

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Author Contributions

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Disclosures

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Table 1. Cumulative Overall Response and Disease Control Rates per RECIST v1.1 by Central Review in Patients With PD-L1 Expression in ≥1% of Tumor Cells as Assessed by a Prototype Assay

	Pembrolizumab 2 mg/kg (n = 55)	**Pembrolizumab 10 mg/kg (n = 280)**
ORR, % (95% CI)[a]		
9 weeks	11.5 (5.3-23.8)	8.4 (5.6-12.3)
18 weeks	13.4 (6.6-26.2)	17.5 (13.5-22.6)
27 weeks	15.7 (8.1-29.0)	19.8 (15.5-25.0)
DCR, % (95% CI)[a]		
9 weeks	41.8 (30.1-55.9)	24.6 (20.0-30.2)
18 weeks	50.9 (38.6-64.6)	48.2 (42.5-54.2)
27 weeks	50.9 (38.6-64.6)	48.9 (43.2-55.0)

CI, confidence interval; DCR, disease control rate; ORR, overall response rate; RECIST v1.1, Response Evaluation Criteria in Solid Tumors version 1.1.

[a]From the Kaplan-Meier method for censored data. Patients who died without undergoing ≥1 postbaseline imaging assessment were considered to be nonresponders.

Table 2. Adverse Event Summary and Duration of Follow-Up by Dose and Schedule in All Patients With NSCLC Treated in KEYNOTE-001 (N = 550)

AE, n (%)	**2 mg/kg Q3W (n = 61)**	**10 mg/kg Q3W (n = 287)**	**10 mg/kg Q2W (n = 202)**
Treatment related			
Any grade	31 (50.8)	201 (70.0)	148 (73.3)
Grade 3-5	5 (8.2)	34 (11.8)	19 (9.4)
Leading to discontinuation	4 (6.6)	11 (3.8)	8 (4.0)
Leading to death	1 (1.6)	1 (0.3)	0 (0.0)
Of special interest based on immune etiology	9 (14.8)	39 (13.6)	32 (15.8)
Duration of follow-up, mo, median (range)	7.7 (6.4-22.7)	16.1 (10.0-32.3)	15.5 (10.0-20.4)

AE, adverse event; Q2W, every 2 weeks; Q3W, every 3 weeks.

Figure 1. Percentage change from baseline in tumor size at 18 weeks by pembrolizumab exposure in evaluable patients with previously treated NSCLC. $AUC_{ss\text{-}6wk}$ is presented in µg * day/mL. The sample size per group is shown and lines extending vertically from the boxes (whiskers) indicate variability outside the 25th and 75th quantile. The ends of the whiskers correspond to the 5th and 95th quantiles of the observed data. All patients treated at 2 mg/kg are in the left-most bin. $AUC_{ss\text{-}6\ wk}$, area under the concentration-time curve at steady state over a 6-week interval; CI, confidence interval.

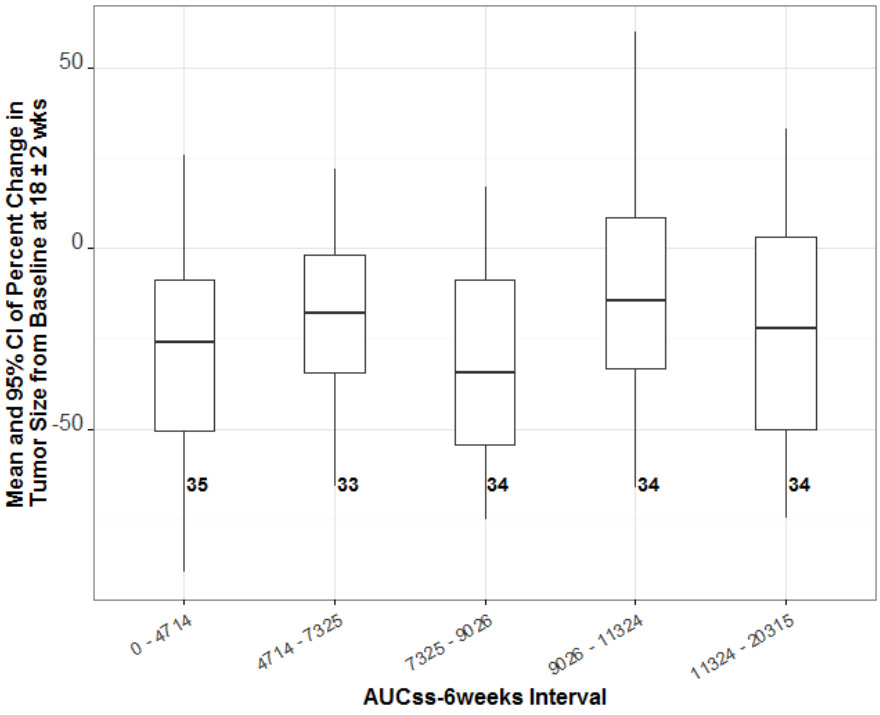

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Figure 2. Percentage change in tumor size from baseline at 18 weeks by pembrolizumab exposure, stratified by PD-L1 status. Clockwise from top left: PD-L1 expression in ≥ 50% of tumor cells, PD-L1 expression in 1-49% of tumor cells, unknown PD-L1 expression, PD-L1 expression in <1% of tumor cells. PD-L1 expression was assessed using a clinical trial immunohistochemistry assay. Circles show 10 mg/kg Q2W, triangles 10 mg/kg Q3W, and squares 2 mg/kg Q3W. The black lines show the linear regression of change in tumor size from baseline vs. $AUC_{ss\text{-}6wk}$. Estimates of the slope and the intercept are presented along with the *P* value of the slope being different from 0 and r^2.

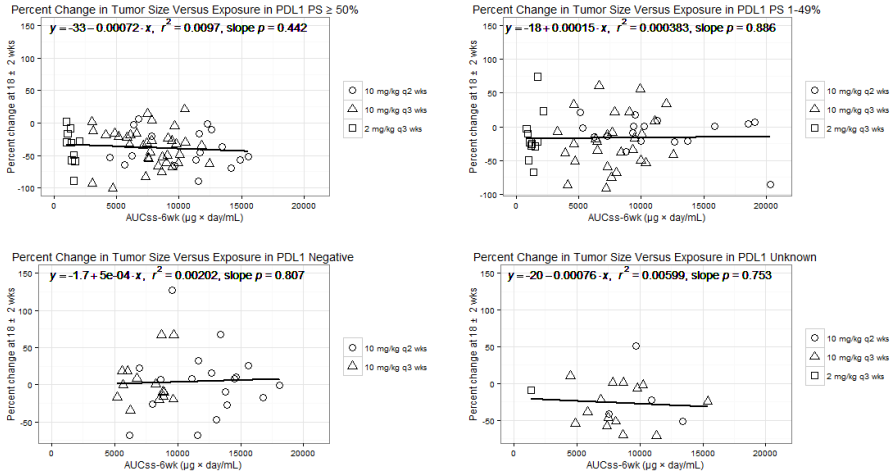

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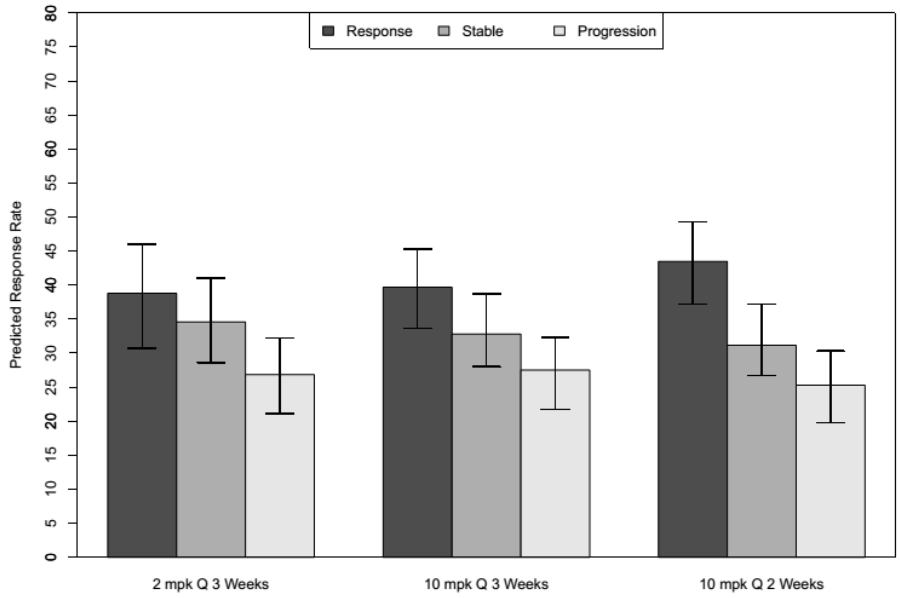
Figure 3. Median simulated response rates at week 27 by AUC groups spanning the observed range of NSCLC exposure (1000 simulated trials, each with 1000 patients). **A.** Patients with PD-L1 expression in ≥50% of tumor cells. **B.** PD-L1 expression in 1-49% of tumor cells. PD-L1 expression was assessed using a clinical trial immunohistochemistry assay. Error bars represent the 90% confidence intervals around the estimates. Response was defined as a ≥30% increase from baseline in SLD, stable disease was defined as change from baseline in SLD, and progression was defined as a ≥20% increase from baseline in SLD). $AUC_{ss\text{-}6\ wk}$, area under the concentration-time curve at steady state over a 6-week interval; CI, confidence interval; SLD, sum of the longest diameters.

A.



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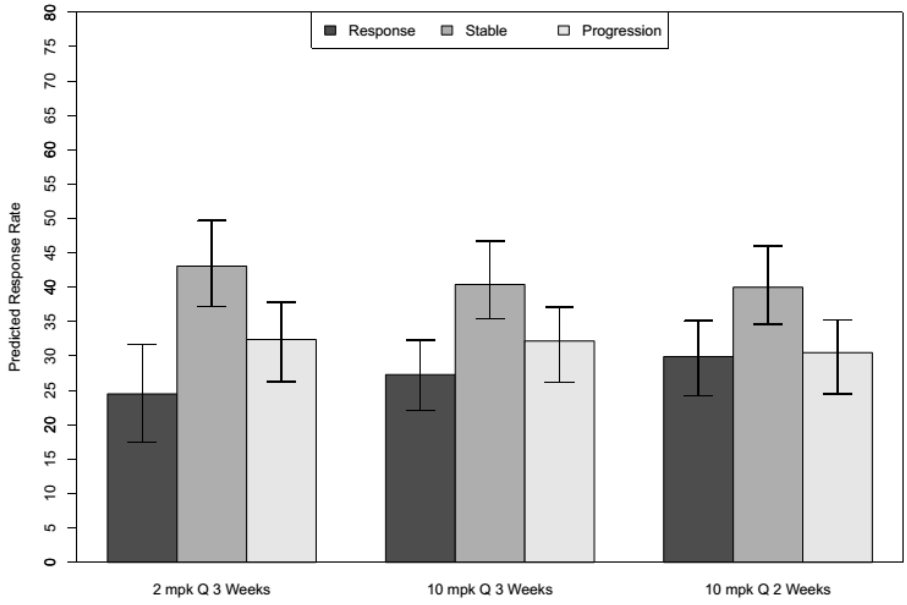
Response
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Progression
Predicted Response Rate
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2 mpk Q 3 Weeks
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Supplementary Table. Categories of adverse events of special interest based on their immune etiology that were considered in the analysis of the relationship between pembrolizumab exposure and safety.

Adrenal insufficiency	Myositis
Autoimmune pancytopenia	Neuropathy
Colitis	Pancreatitis
Drug-induced liver injury	Pericarditis
Hemolytic anemia	Pneumonitis
Hepatitis	Renal failure and nephritis
Hypophysitis	Severe skin reactions
Hyperthyroidism	Thyroiditis
Hypothyroidism	Type 1 diabetes mellitus
Infusion reaction	Uveitis
Myasthenic syndrome	Vasculitis
Myocarditis	

Adverse events were considered regardless of grade of severity with the exception of severe skin reactions; for pruritus, rash, generalized rash, and maculopapular rash, only events of grade ≥3 severity were considered to be adverse events of special interest.