ORIGINAL ARTICLE

Quantitative Characterization of the Exposure–Response Relationship for Cancer Immunotherapy: A Case Study of Nivolumab in Patients With Advanced Melanoma

X Wang1*, Y Feng1, G Bajaj1, M Gupta1, S Agrawal1, A Yang2, J-S Park3, B Lestini2 and A Roy1

To inform the benefit–risk assessment of nivolumab in patients with advanced melanoma, analyses of efficacy and safety exposure–response (E–R) relationships were conducted with data from patients with advanced melanoma enrolled in two clinical studies (phase I and phase III) who received nivolumab 0.1–10.0 mg/kg every 2 weeks. E-R efficacy analyses were performed by relating the nivolumab time-averaged concentration after the first dose ($C_{avg1}$) to two endpoints: RECIST objective response (OR) and overall survival (OS). E–R safety analyses characterized the relationship between nivolumab $C_{avg1}$ and the hazard of all-causality adverse events leading to discontinuation or death (AE-DC/D). Nivolumab exposure represented by $C_{avg1}$ was not a significant predictor of OR, OS, or the hazard of AE-DC/D. E–R efficacy and safety relationships were relatively flat over the exposure range.

CPT Pharmacometrics Syst. Pharmacol. (2017) 6, 40–48; doi:10.1002/psp4.12133; published online 26 December 2016.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
- Nivolumab is a novel immuno-oncology (I-O) agent that inhibits tumor-mediated PD-L1 signaling. The exposure–response relationship has not been previously characterized for nivolumab.

WHAT QUESTION DOES THIS STUDY ADDRESS?
- This analysis defined the benefit–risk for an I-O compound by incorporating the exposure–response relationship for nivolumab for safety and efficacy in melanoma. Results demonstrated a flat E–R relationship across a wide exposure range.

WHAT THIS STUDY ADDS TO OUR KNOWLEDGE
- This analysis provided a quantitative way to characterize the benefit–risk profile of nivolumab, in which typical E–R analysis methods were applied to an I-O agent with a novel mechanism of action.

HOW MIGHT THIS CHANGE DRUG DISCOVERY, DEVELOPMENT, AND/OR THERAPEUTICS?
- This analysis contributed to the approval of nivolumab for advanced melanoma. The favorable benefit–risk profile at the approved dose regimen was supported by this analysis.

Tumors evade detection and removal by the adaptive immune system by exploiting pathways that regulate immune responses and maintain immune tolerance in normal tissues. These immune checkpoint pathways are appealing targets for anticancer therapy, and several immune checkpoint inhibitors that modulate different pathways have either been approved or are in late-stage clinical development for the treatment of multiple tumor types.1

Programmed death-1 (PD-1) is an immune inhibitory molecule that plays an important role in regulating T-cell-mediated immune responses in peripheral tissues. PD-1 is a cell surface receptor expressed on activated T cells that has two known ligands (PD-L1 and PD-L2), which are normally displayed on antigen-presenting cells. Binding of either ligand with PD-1 inhibits T-cell receptor signaling, downregulates expression of apoptotic molecules, and affects the cell cycle.2 Cell surface expression of PD-L1 has also been observed in many tumor types and is thought to contribute to tumor cell immune evasion.3–10

Moreover, the presence of PD-L1 on tumor cells has been shown to be associated with poor clinical outcomes in patients with multiple types of cancer.11–14 Thus, blocking tumor-mediated PD-L1 signaling can lead to reactivation of T cells against tumor antigens.

Nivolumab (Opdivo, Bristol-Myers Squibb, New York, NY, and Ono Pharmaceuticals, Trenton, NJ) is a fully human immunoglobulin G4 monoclonal antibody that has a high affinity for PD-1.15 In patients with solid tumors, more than 70% of PD-1 molecules on circulating T cells were occupied by nivolumab for ≥2 months after intravenous infusion of single doses between 0.3 and 10.0 mg/kg.15 Nivolumab has been shown to produce durable objective responses (ORs) by Response Evaluation Criteria in Solid Tumors (RECIST) criteria in patients with solid tumors and relapsed or refractory Hodgkin’s lymphoma in phase I clinical trials.16,17 in patients with renal cell carcinoma (RCC), and in patients with non-small cell lung cancer (NSCLC) in phase II trials.18,19 In addition, nivolumab has demonstrated an
overall survival (OS) benefit in pivotal studies in several tumor types.\textsuperscript{20–24} When administered at a dose of 3.0 mg/kg every 2 weeks (Q2W) in phase III trials, nivolumab produced significantly higher OR rates than conventional chemotherapy among patients with melanoma that had progressed after ipilimumab therapy\textsuperscript{25} and significantly longer OS than conventional chemotherapy among previously untreated patients with melanoma.\textsuperscript{26} Nivolumab was well tolerated in clinical trials over the dosage range of 0.1–10.0 mg/kg.\textsuperscript{15,19,22,23,25,26} Among patients with melanoma treated with a dose of 3.0 mg/kg Q2W, a total of 12% of patients experienced grade 3 or 4 adverse events (AEs) and 6% of patients discontinued treatment because of AEs.\textsuperscript{26} Nivolumab is currently approved for the treatment of patients with previously treated unresectable or metastatic melanoma, patients with previously treated metastatic NSCLC, patients with advanced RCC, patients with classical Hodgkin’s lymphoma, and in combination with ipilimumab for the treatment of unresectable or metastatic melanoma.\textsuperscript{27,28}

As a cancer immunotherapy with a novel mechanism of action, the exposure–Response (E–R) relationship of nivolumab is of special interest to better understand its benefit–risk profile. This article describes nivolumab E–R analyses of efficacy and safety in patients with advanced melanoma.

METHODS
Study designs and treatment
Three E–R analyses were conducted to examine the relationship between nivolumab exposure and efficacy/safety responses in patients with advanced melanoma. All analyses used data collected in the following two clinical studies: CA209003 (a phase I dose-escalation study in which patients with solid tumors received intravenous nivolumab 0.1, 0.3, 1.0, 3.0, or 10.0 mg/kg Q2W; ClinicalTrials.gov identifier: NCT00730639\textsuperscript{16,23}; patients who received 0.1 and 0.3 mg/kg were eligible to receive 1 mg/kg based on investigator assessment) and CA209037 (an open-label, international, phase III study in which patients with advanced melanoma were randomized to receive either nivolumab 3.0 mg/kg Q2W or the investigator’s choice of an alternative regimen (dacarbazine or carboplatin plus paclitaxel); NCT01721746).\textsuperscript{25} CA209003 enrolled patients with metastatic castrate–Resistant prostate cancer, RCC, colorectal adenocarcinoma, malignant melanoma, or NSCLC, but only data from the melanoma cohort were included.

Only patients with both nivolumab exposure data and either IRRC-assessed (CA209037) or investigator-assessed (CA209003) OR were included in the E–R efficacy analyses (OR and OS). All patients with nivolumab exposure data were included in the E–R safety analysis. An overview of the two trials included in both analyses is provided in Supplementary Table 1.

The studies were approved by local Institutional Review Boards and independent ethics committees and were carried out in accordance with the ethical principles of the Declaration of Helsinki. All patients provided informed written consent before undergoing any study-specific procedures.

Exposure measures and response endpoints
A previously developed population pharmacokinetic (PPK) model\textsuperscript{29} was applied to provide each patient’s measure of nivolumab exposure for the E–R analyses.

In the efficacy analysis of OR, the PPK model predicted nivolumab time-averaged concentration after the first dose (\(C_{\text{avg}1}\)) was used as the measure of nivolumab exposure, as it is a relevant measure of exposure that would have been experienced by all patients who received even a single dose of nivolumab and it would have been experienced by all patients who received nivolumab prior to their efficacy (OR) assessment. In addition, the PPK model showed that nivolumab clearance was time-dependent.\textsuperscript{30} Therefore, steady-state exposure might be affected by decreasing clearance over time and potentially be confounded with disease status change. The efficacy response endpoint of an OR was defined as a confirmed complete response (CR) or partial response (PR). Response status in study CA209037 was based on RECIST 1.1 criteria as assessed by an IRRC, and response criteria in study CA209003 was based on RECIST 1.0 as determined by investigators. The same exposure measurement of \(C_{\text{avg}1}\) was used in the E–R analysis of OS. The results of the analyses are not expected to be sensitive to the summary measure of early nivolumab exposure, as they are highly correlated (\(R = 0.95\) for correlations between \(C_{\text{avg}1}\) and trough concentration after the first dose (\(C_{\text{min}1}\)). The response endpoint was the time from the start of nivolumab treatment to death. In the safety analysis, the PPK model-predicted \(C_{\text{avg}1}\) was used as the measure of nivolumab exposure for the same reason as stated above. The safety outcome of interest was the time to occurrence of all-causality discontinuation or death (AE-DC/D). Time to onset of an AE was defined as the time between the first day of nivolumab treatment and the onset date of the AE-DC/D. If a patient did not experience an AE-DC/D, the time to onset was censored at either the last treatment date plus 100 days (i.e., the safety follow-up period per protocol) or the date the patient was last known to be alive, whichever occurred first.

E–R analysis of efficacy
Objective response. The association between nivolumab \(C_{\text{min}1}\) and the probability of achieving an OR (Pr(OR)) in patients with advanced melanoma was examined by a logistic regression model. Development of the model proceeded in two stages. A base model was first developed to assess the existence and functional form of the relationship between nivolumab \(C_{\text{avg}1}\) and Pr(OR). Second, the impact of baseline covariate and exposure on Pr(OR) was examined in a full model. Baseline covariates considered as categorical variables included prior anti-CTLA-4 treatment (yes vs. no (comparator vs. reference group)), sex (female vs. male), and Eastern Cooperative Oncology Group (ECOG) performance status (\(\geq 1\) vs. 0). Baseline covariates considered as continuous variables included body weight, tumor burden (calculated as the sum of longest diameters of all target lesions), and baseline serum lactate dehydrogenase (LDH) level. Baseline LDH was normalized to the upper limit of normal to account for differences in the normal range across clinical laboratories at which LDH was measured.
The log-transformed LDH values were incorporated into the model. The full model incorporated all covariates and exposure effects simultaneously.

The covariates were selected based on their previous identification as either known prognostic factors in advanced melanoma (ECOG performance status, sex, and baseline LDH)31,32 or their representation of potential prognostic factors of particular interest (prior anti-CTLA-4 treatment, baseline tumor burden, and body weight). Two other covariates of interest (PD-L1 expression status and prior benefit from anti-CTLA-4 therapy) could not be assessed in this analysis due to a high proportion of missing PD-L1 expression values and no prior exposure to anti-CTLA-4 therapy in study CA209003.

Model performance was assessed by visual predictive check (VPC), comparing the observed proportion of OR with the corresponding model-predicted 90% prediction intervals of OR, determined by simulation (1,000 iterations) with model-estimated Pr(OR) for each patient in the analysis dataset.

**E-R analysis of efficacy**

**Overall survival.** The E-R analysis of OS characterized the hazard ratio (HR) of OS with respect to nivolumab C avg1 and selected covariates by a Cox proportional hazard (CPH) model. The relationship was assessed by a full model, which incorporated the covariates assessed in the E-R of OR as described above. An additional covariate assessed was the effect of nivolumab baseline clearance, as it has previously been shown to be an important predictor of OS among patients treated with monoclonal antibodies (bevacizumab, trastuzumab, and nivolumab).33,34 The correlation between C avg1 and baseline clearance is low (correlation coefficient, 0.18), mostly due to the fact that analysis data included a wide range of doses (0.1–10.0 mg/kg). Therefore, the effects of both nivolumab C avg1 and baseline clearance were not expected to be highly confounded and could be estimated simultaneously.

The CPH models were evaluated by VPC, comparing the model-predicted cumulative time-to-event distributions (from 1,000 simulations) with the corresponding distribution determined by nonparametric Kaplan–Meier analysis. The CPH model-predicted survival curve for each patient was used to simulate the occurrence of events and subsequently calculate the cumulative time-to-event distribution.

**E-R analysis of safety**

The association between nivolumab C avg1 and the HR of AE-DC/D was also characterized by a CPH model. The model was developed in two stages, similar to that used in the efficacy analysis described above. First, the relationship between nivolumab C avg1 and time to event was characterized in a base CPH model. Next, a full model was developed by incorporating the effects of baseline covariates in addition to nivolumab exposure.

The full model included the following categorical covariates at baseline: anti-CTLA-4 treatment (yes vs. no (comparator vs. reference group)), sex (female vs. male), and ECOG performance status (≥1 vs. 0). The continuous covariates included were age, body weight, and baseline LDH. The same method of model evaluation as in the E-R analysis of OS was used to assess the model performance for predicting the observed time to event.

**RESULTS**

The E-R analyses included patients with advanced melanoma who received nivolumab 0.1 to 10.0 mg/kg Q2W in studies CA209003 and CA209037. Data from 221 patients with evaluable OR and OS results were included in the E-R analysis of efficacy. The E-R analysis of safety included data from 336 patients for whom nivolumab exposure measures were available. The baseline characteristics of these patients are presented in Table 1, and brief descriptions of these studies are provided in the Methods section.

**E-R analysis of efficacy**

**Objective response.** Of the patients with advanced melanoma included in the efficacy analysis of OR, 70 (31.7%) experienced an OR (complete response (CR), n = 5; partial response (PR), n = 65).

The effect of the PPK model-predicted time-averaged C avg1 and covariates in the full logistic regression model on the odds of achieving OR are presented in Figure 1. The odds of OR was related to log(C avg1), which was not a significant predictor (95% confidence interval (CI) includes unity). The covariates evaluated were also not significant.
predictors of OR, although there was a trend toward a decrease in probability of OR with increasing baseline tumor burden (odds ratio, 0.765; 95% CI, 0.51–1.15).

A VPC of the model-predicted marginal probability of OR with respect to C avg1 is provided in Figure 2. The observed proportion of responders is consistent with the corresponding model-predicted proportions. The undulating pattern in the predicted marginal probability of OR vs. C avg1 is due to the effect of covariates other than Cavg1 on the probability of OR.

E–R analysis of efficacy

Overall survival. Figure 3 presents the estimated effects of C avg1 and covariates on the HR of OS in the full CPH model. Nivolumab baseline clearance, baseline body weight, and baseline LDH were significant predictors of OS (95% CI does not include unity). The hazard of death increased with increasing nivolumab clearance, increasing LDH, and decreasing body weight. Nivolumab C avg1 was not a significant predictor of OS, after accounting for the effect of these covariates included in the full model (95% CI includes

Figure 1 Effect of nivolumab exposure (C avg1) and selected covariates on odds ratio of objective response. CI, confidence interval; C avg1, model-predicted average concentration after the first dose; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

Figure 2 Marginal probability of OR versus nivolumab C avg1 (visual predictive check). Note: The horizontal box shows the median and interquartile range of C avg1, and the whiskers show the 5th/95th percentiles of C avg1. C avg1, model-predicted time-averaged concentration after the first dose; OR, objective response; PI, prediction interval.
The PPK analysis has shown that nivolumab clearance increases with increasing body weight and the two variables are hence correlated. The directions of their relationships to OS are opposite, and the correlation between the two estimated effects is $-0.27$, indicating that the effects from these two predictors are not confounded.

The VPC of model-predicted mean (90% CI) OS by dose level is consistent with the observed OS based on Kaplan–Meier analysis for doses ranging from 0.1 to 10.0 mg/kg (Figure 4).

A sensitivity analysis (excluding the effect of clearance) was performed to assess the potential confounding effect of $C_{avg1}$ by nivolumab baseline clearance; however, the effect of $C_{avg1}$ remained nonsignificant (95% CI includes unity) (Supplementary Figure S1).

Figure 3 Effect of nivolumab $C_{avg1}$ and selected covariates on hazard ratio of overall survival (full model). $C_{avg1}$, model-predicted time-averaged concentration after the first dose; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

DISCUSSION

The development of cancer immunotherapy agents—characterized by their unique, immune-based mechanisms of action—is evolving and can be facilitated by quantitative analyses, such as those presented in this article. These findings are based on analyses of data combined from two

E–R analysis of safety

There were 37 AEs leading to discontinuation or death (AE-DC/D) among the patients with advanced melanoma included in this analysis (including one AE leading to death). The estimated effects of $C_{avg1}$ and covariates on the risk of AE-DC/D in the full CPH model are shown in Figure 5. Nivolumab $C_{avg1}$ was not a significant predictor of the risk of AE-DC/D; however, the HR of AE-DC/D increased with higher baseline LDH levels. The VPC of model-predicted cumulative probability of AE-DC/D by dose level was in agreement with the corresponding curves determined by Kaplan–Meier analysis, indicating adequate model performance (Figure 6).
clinical trials (one phase I and one phase III) in patients with advanced melanoma, and thus this analysis is specific to melanoma. Although uniform dosing is expected to be applicable across cancer histologies based on the mechanism of action of nivolumab, data from patients with other tumor types were not included in the efficacy analysis because of the tumor type-specific OR assessment. A previous analysis suggested a tumor type difference in AE-DC/D risk, but the E–R safety relationships were flat in patients with both melanoma and NSCLC.35

PPK model-predicted Cavg1 was used in the E–R analysis of efficacy and safety. The predictions of this exposure measure are considered adequate for the purpose of E–R characterization, based on the PPK model diagnostics and evaluations. The ETA shrinkage of clearance and central volume of distribution are 14.2% and 13.4%, respectively, and the EPS shrinkage is 15.5%.30 Therefore, the individual pharmacokinetic (PK) parameters, and hence the exposure measures, are adequately characterized. Nivolumab Cavg1 was selected as the measure of exposure for the characterization of E–R relationships of both efficacy (OR and OS) and safety (AE-DC/D). It reflects the average exposure prior to the occurrence of the majority of events and was available in all patients who received nivolumab treatment. In addition, the developed PPK model described a trend of nivolumab clearance changing with time; hence, the PK is time-varying. This could be due to the potential effect of changes in disease status on PK. Therefore, using the early exposure measurement of Cavg1 could avoid such a confounding effect in the characterization of causal E–R relationships. It is expected that the E–R relationship of Cavg1 is similar to that of other early exposure, such as Cprev1, as these summary measures are highly correlated.

The findings of the presented analyses are consistent with that of an earlier analysis, which indicate a flat E–R relationship, and identified significant predictors for both efficacy and safety.28,29,32,36

Specifically, among the markers of disease status (baseline tumor burden, ECOG performance status, and LDH), none had a significant impact on OR rates. Two other covariates of interest (PD-L1 expression and prior benefit from anti-CTLA-4 therapy) could not be assessed in either analysis due to the high proportion of missing values. However, both of these covariates were assessed in a separate E–R analysis of OR using only data from the phase III study (CA209037), where nivolumab E–R relationship was flat with nivolumab 3.0 mg/kg Q2W, and there was no association between prior benefit from anti-CTLA-4 therapy and OR, but the estimated odds of OR was higher for patients with PD-L1 expression (>5%) by an immunohistochemical assay, relative to <5% or indeterminate expression status.36 The possible association between PD-L1 status and the early efficacy outcome (OR) is consistent with the results from a study in patients with solid tumors (including melanoma) in which higher levels of PD-L1 expression may correlate with OR.16,26

Results from the E–R analysis of OS suggested that nivolumab baseline clearance, baseline body weight, and LDH were the strongest predictors of OS, whereas there was no significant association between nivolumab exposure and OS. Baseline body weight is an indicator of cancer severity, and similarly, elevated baseline LDH is associated with poor prognosis in patients with melanoma.37 It is possible that a patient’s ability to clear nivolumab also reflects his/her overall disease state. This is supported by findings from a PPK analysis that higher ECOG performance status was associated with higher nivolumab baseline clearance.29 The PPK analysis also showed that nivolumab clearance is time-varying. Considering that the change of clearance is potentially associated with changes in patients’ disease
state, the baseline clearance was used in the E–R analysis to avoid confounding effects on OS.

It is noted that the efficacy analysis evaluated association between nivolumab exposure and both OR rate and OS. Besides effectiveness over time, these two endpoints have different measurements. OR reflects tumor burden reduction, while OS is considered a gold-standard endpoint of clinical benefit. Findings of the lack of E–R relationship were generally consistent for both endpoints. There appeared to be a differential impact of baseline prognostic factors on OS and OR, such as baseline body weight and LDH. Such differences are not unexpected. Based on a meta-analysis of randomized, active-controlled trials, although there were indications of a strong correlation between OR rate and progression-free survival, such correlation between OR rate and OS was not established.38

Figure 5 Effect of nivolumab $C_{avg1}$ and selected covariates on hazard ratio of adverse events leading to discontinuation or death (full model). $C_{avg1}$, model-predicted time-averaged concentration after first dose; CI, confidence interval; CTLA-4, cytotoxic T-lymphocyte-associated antigen 4; ECOG, Eastern Cooperative Oncology Group; LDH, serum lactate dehydrogenase; PS, performance status; ULN, upper limit of normal.

Specifically, the versions of RECIST criteria were different (v. 1.0 and 1.1 for CA209003 and CA209037, respectively), and the OR reported in CA209003 was sponsor-derived, whereas the OR reported for CA209037 was assessed by an Independent Radiology Review Committee (IRRC). Nevertheless, similar response rates were observed in the two studies despite the different assessment methodologies, which supported the data pooling for the E–R analysis.

The selected safety characteristic of AE-DC/D was chosen to reflect a broad range of event types that may prevent patients from receiving treatment. Another safety endpoint of grade $CPT: Pharmacometrics & Systems Pharmacology$

state, the baseline clearance was used in the E–R analysis to avoid confounding effects on OS.

It is noted that the efficacy analysis evaluated association between nivolumab exposure and both OR rate and OS. Besides effectiveness over time, these two endpoints have different measurements. OR reflects tumor burden reduction, while OS is considered a gold-standard endpoint of clinical benefit. Findings of the lack of E–R relationship were generally consistent for both endpoints. There appeared to be a differential impact of baseline prognostic factors on OS and OR, such as baseline body weight and LDH. Such differences are not unexpected. Based on a meta-analysis of randomized, active-controlled trials, although there were indications of a strong correlation between OR rate and progression-free survival, such correlation between OR rate and OS was not established.38

It should be noted that, although the OR in the two clinical studies were pooled for purposes of this E–R analysis, the methods of assessing OR differed slightly for each.
all causality to avoid subjectivity in assessing AE causality. Malignant neoplasm progression and metastases were not included due to their clear attribution to disease progression, which was not the intention of the E–R safety analysis. Nivolumab exposure, as indicated by Cavg1, did not have a statistically significant or clinically relevant effect on AE-DC/D. The lack of a clinically significant exposure effect was consistent with the overall manageable safety profile of nivolumab monotherapy observed across the dose range of 0.1–10.0 mg/kg Q2W evaluated in the phase I multidose, dose–escalation study.

Baseline LDH level was examined as a potential modulatory factor of the E–R safety relationship, and the findings suggested that the elevation of baseline LDH was associated with a higher burden of safety events.

In conclusion, the present work highlights the application of quantitative clinical pharmacology to the development of the novel immuno-oncology agent nivolumab. As a member of the new class of checkpoint inhibitors, nivolumab has a unique mechanism of action; hence, it is important to understand the relationship between its pharmacologic and benefit–risk profiles. The safety and efficacy profiles of nivolumab are not affected by nivolumab serum concentrations in patients with advanced melanoma across the dose range of 0.1 to 10.0 mg/kg Q2W. The selection of 3 mg/kg was based on the totality of efficacy and safety data collected in the phase I study (CA209003). In particular, nivolumab was safe and tolerable up to 10 mg/kg, and there were more ORs observed in patients with melanoma and NSCLC treated with doses of nivolumab 3 mg/kg and 10 mg/kg than with nivolumab 1 mg/kg.

Acknowledgments. The authors thank Neelima Thanneer, Prema Sukumar, and Erin Dombrowsky for their support of analysis dataset preparation. This analysis was funded by Bristol-Myers Squibb (Lawrenceville, NJ, USA). Editorial support was provided by Blair Jarvis of inScience Communications, Springer Healthcare (Philadelphia, PA, USA), funded by Bristol-Myers Squibb (Lawrenceville, NJ, USA).

Conflict of Interest/Disclosure. X.W. and A.R. are employees of and hold stock in Bristol-Myers Squibb. Y.F., G.B., M.G., S.A., A.Y., J.-S.P., and B.L. are all employees of Bristol-Myers Squibb.

Author Contributions. X.W. wrote the article; M.G., S.A., A.Y., J-S.P., B.L., and A.R. designed the research; X.W., Y.F., and G.B., performed the research; M.G., S.A., A.Y., J-S.P., B.L., and A.R. analyzed the data.

1. Shih K., Arkenau, H.T. & Infante, J.R. Clinical impact of checkpoint inhibitors as novel cancer therapies. Drugs 74, 1993–2013 (2014).
2. Keir M.E., Butte, M.J., Freeman, G.J. & Sharpe, A.H. PD-1 and its ligands in tolerance and immunity. Annu. Rev. Immunol. 26, 677–704 (2008).
3. Dong H. et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. Nat. Med. 8, 793–800 (2002).
4. Iwai Y., Ishida, M., Tanaka, Y., Okazaki, T., Honjo, T. & Minato, N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. Proc. Natl. Acad. Sci. U. S. A. 99, 12293–12297 (2002).
5. Azuma T., Yao, S., Zhu, G., Fliex, A.S., Fliex, S.J. & Chen, L. B7-H1 is a ubiquitous antiapoptotic receptor on cancer cells. Blood 111, 3635–3643 (2008).
6. Wilcox R.A. et al. B7-H1 (PD-L1, CD274) suppresses host immunity in T-cell lymphoproliferative disorders. Blood 114, 2149–2158 (2009).
7. Yamamoto R. et al. PD-1-PD-1 ligand interaction contributes to immunosuppressive microenvironment of Hodgkin lymphoma. Blood 111, 3220–3224 (2008).
8. Chen B.J. et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clin. Cancer Res. 19, 3462–3473 (2013).
9. Frigola X. et al. Identification of a soluble form of B7-H1 that retains immunosuppressive activity and is associated with aggressive renal cell carcinoma. Clin. Cancer Res. 17, 1915–1923 (2011).
10. Baral A., Ye, H.X., Jiang, P.C., Yao, Y. & Mao, Y. B7-H3 and B7-H1 expression in cerebral spinal fluid and tumor tissue correlates with the malignancy grade of glioma patients. OncoLett. 8, 1195–1201 (2014).
Supplementary information accompanies this paper on the CPT: Pharmacometrics & Systems Pharmacology website (http://psp-journal.com)