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Priority Brief

Cancer Immunology Research

Prolonged Benefit from Ipilimumab Correlates with Improved Outcomes from Subsequent Pembrolizumab

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Abstract

Patients with metastatic melanoma whose disease progresses on ipilimumab can clearly derive benefit from subsequent anti–programmed death-1 (PD-1). However, patients experience heterogeneous outcomes with ipilimumab, including rapid or delayed progression, and it is unclear whether patterns of ipilimumab progression influence subsequent clinical responses to anti–PD-1. We retrospectively reviewed data from 116 patients with metastatic melanoma who progressed on ipilimumab and were subsequently treated with pembrolizumab. The study objectives were to determine whether progression-free survival (PFS) with ipilimumab was associated with PFS, objective response rate (ORR), and clinical benefit rate (CBR; ORR + stable disease) with pembrolizumab. Patients with PFS $\geq$90 days after treatment with ipilimumab generally had superior outcomes with subsequent pembrolizumab treatment compared with patients with PFS <90 days (ORR, 49% vs. 35%, $P = 0.12$; CBR, 66% vs. 46%, $P = 0.03$). Patients with prolonged ipilimumab benefit (PFS $\geq$ 180 days) had excellent outcomes with pembrolizumab compared with rapid progressors (PFS < 45 days; ORR, 55% vs. 25%; CBR, 80% vs. 25%; median PFS, 249 vs. 50 days). Using logistic regression models, PFS with ipilimumab was independently correlated with response to pembrolizumab (odds ratio, 1.22; 95% CI, 1.02–1.51). This study shows that prolonged PFS with ipilimumab predicts excellent outcomes with subsequent pembrolizumab treatment, offering valuable prognostic information for clinicians. *Cancer Immunol Res; 4(7); 569–73. ©2016 AACR.*

Introduction

The advent of more effective and less toxic immune therapies has revolutionized therapy for patients with metastatic melanoma. Once among the most recalcitrant and therapy-resistant of all cancers, melanoma has been at the leading edge in both immune and genetically targeted therapy advances. We are now faced with choosing between multiple effective therapies and identifying the most optimal treatment sequences.

Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), was the first agent to improve survival in metastatic melanoma (1, 2). Although the objective response rate (ORR) is low, nearly 20% of patients survive for 5 years, findings that greatly improved from outcomes with historical controls (3, 4). Anti–PD-1-directed therapies have higher response rates than ipilimumab and also appear to produce durable responses (5, 6). Two of these agents, pembrolizumab and nivolumab, have received regulatory approval for use when patients progress after ipilimumab treatment (7, 8). More recently, both agents have demonstrated superiority to ipilimumab in patients naïve to both drugs and have now received regulatory approval in this setting (9, 10).

Although anti–PD-1 agents have now become the standard first-line immune therapy in most cases, a sizable number of patients have received or will receive ipilimumab as initial therapy. Because most of these patients treated with ipilimumab will ultimately experience disease progression, additional therapy will be required. Whereas both pembrolizumab and nivolumab have demonstrated clinical activity in patients who experienced disease progression on ipilimumab, it is unknown whether the pattern of progression on ipilimumab influences subsequent outcomes from anti–PD-1 treatment. We hypothesized that some patients possess an "immune-unresponsive phenotype," and if they rapidly progress on ipilimumab, they are less likely to derive benefit from anti–PD-1 therapies. Therefore, we speculated that the duration of benefit from ipilimumab would correlate with subsequent response to anti–PD-1 [e.g., patients with prolonged progression-free survival (PFS) after treatment with ipilimumab would tend to respond to subsequent anti–PD-1 and *vice versa*]. Identifying this association could provide valuable prognostic information and may help stratify patients unlikely to benefit from immune therapy toward other treatment modalities (e.g., targeted therapy).

To investigate this question, we conducted a retrospective study of patients at Mayo Clinic (Jacksonville, FL) and Vanderbilt University (Nashville, TN) who had been treated sequentially with both ipilimumab and pembrolizumab from 2011 to January 2015. The primary objective of this study was to determine whether the duration of PFS with ipilimumab influenced patient outcomes with subsequent pembrolizumab therapy.

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Note: Supplementary data for this article are available at Cancer Immunology Research Online (http://cancerimmunolres.aacrjournals.org/).

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Materials and Methods

Patients

After approval by the Institutional Review Board, the clinical data from 116 patients from May 2011 through January 2015 who received treatment with ipilimumab and pembrolizumab at Mayo Clinic ($n = 76$) and Vanderbilt University ($n = 40$) were collected. All patients who received at least one dose of both ipilimumab and pembrolizumab were included in the analysis. At the time of analysis, all surviving patients had been followed for a minimum of 80 days after treatment with pembrolizumab. For this study, we included only patients who received therapy sequentially; we did not include patients treated with combined ipilimumab and nivolumab.

Study design

Demographic data including age, sex, site of metastatic disease, and lactate dehydrogenase (LDH) values were recorded. We collected treatment results, including objective response (by RECIST 1.1 criteria), PFS, and overall survival (OS) for each therapy (11). The interval between ipilimumab and pembrolizumab therapy was also recorded. Tumor response was assessed by cross-sectional imaging after four cycles of ipilimumab, unless deterioration necessitated imaging before all cycles were completed. Ipilimumab was administered at the FDA-approved dose of 3 mg/kg. Pembrolizumab was administered at 2 mg/kg every 3 weeks as standard therapy or part of an expanded access program, or at various doses (2–10 mg/kg every 2–3 weeks) through clinical trials.

Statistical analysis

PFS was calculated as the time from the first dose of therapy to the date of documented disease progression and was assessed for ipilimumab and pembrolizumab, respectively. OS was calculated as the time from therapy start to time of death for any reason. Patients were censored at their last follow-up. Per RECIST 1.1 criteria, complete response (CR) was defined as the resolution of all lesions and the absence of new lesions and partial response (PR) as a decrease in tumor burden by 30% from the baseline measurements. ORR was defined as the rate of CR or PR; clinical benefit rate (CBR) was defined as the aggregate of CR and PR, and stable disease (SD) was defined as disease lasting at least 3 months (CR + PR + SD).

The outcomes with pembrolizumab were assessed in relation to PFS on prior ipilimumab treatment. We assessed PFS with ipilimumab as a continuous variable and correlated it with response to pembrolizumab using ordinal logistic regression models, controlled for age, prior therapies, treatment center, metastatic stage, and LDH. Ordinal regression models considered progressive disease, SD, and objective response (CR/PR) as ordinal outcomes. We also performed Cox proportional hazards analysis controlling for the same variables to determine whether PFS with ipilimumab predicted PFS with subsequent pembrolizumab treatment. We stratified patients with ≥90-day PFS and <90-day PFS and compared their response with subsequent anti–PD-1 using χ^2 testing, and compared subsequent PFS and OS with anti–PD-1 between these two groups using the log-rank test. We performed similar analyses stratifying by more extreme values of ipilimumab PFS of <45 days ("rapid progression") compared with ipilimumab PFS of >180 days ("prolonged benefit"). For proof of concept, we also performed these analyses using cutoffs of 60/120 days and stratifying into tertiles. *P* values in these analyses represented the likelihood of difference between any groups.

Results

Patient characteristics

A total of 116 patients from all Mayo Clinic sites and Vanderbilt University were included in the final analysis. Of these, 37% of patients were female ($n = 42$) and 63% were male ($n = 73$; Table 1). Ages ranged from 24 to 88 years with a mean of 63 years. Some patients (59%, $n = 69$) received no treatment prior to ipilimumab.

Among all patients treated with ipilimumab, the median PFS was 94 days. Of these, 75% ($n = 86$) had progressive disease as their best response to ipilimumab, 6% ($n = 7$) had a PR, and 18% ($n = 21$) had SD. Following treatment with ipilimumab, 67 patients had an interim treatment, whereas the remaining patients were treated with pembrolizumab immediately after progression on ipilimumab. Of all patients then treated with pembrolizumab, 35% ($n = 41$) had a PR, 7% ($n = 8$) had a CR, 14% ($n = 16$) had SD, and 44% ($n = 51$) had primary disease progression on pembrolizumab, with a median PFS of 176 days. The median OS from the time of ipilimumab administration was not reached; at the time of analysis, 67% of patients remained alive ($n = 77$). The median time between ipilimumab and pembrolizumab initiation was 257 days, and the median time of follow-up after starting pembrolizumab was 174 days.

Ipilimumab PFS correlated with subsequent pembrolizumab outcomes

We evaluated whether outcomes to pembrolizumab varied in relation to prior PFS on ipilimumab. We performed a multivariate Cox proportional hazards analysis to control for known prognostic variables: age, metastatic stage, prior therapy, and LDH values. Ipilimumab PFS, as measured in months, was significantly associated with decreased odds of pembrolizumab progression (odds ratio, 0.85; $P = 0.02$). To identify whether particular PFS cutoffs were clinically useful, we stratified patients by PFS with ipilimumab of greater than or less than 90 days. Patients with

Table 1. Patient demographics

	N	%
Gender		
Female	43	37
Male	73	63
Age, y		
24–88	63 (mean)	
Site of metastatic disease		
Liver	28	24
Lung	60	52
Brain	16	14
Bone	17	15
Lymph	49	42
Other	45	39
Lines of treatment prior to ipilimumab		
0	69	59
1	34	29
2+	13	11
LDH at start of ipilimumab	195 (median)	
Lines of interval treatment between ipilimumab and PD-1		
0	59	51
≥1	57	49
Interval radiation	19	16
Interval BRAF inhibitor	22	19
LDH at start of anti-PD-1	238 (median)	
Status at last follow-up		
Alive	77	66
Dead	39	34

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Table 2. Response to pembrolizumab based on PFS with ipilimumab

	Ipilimumab PFS		
	<90 days ($n = 57$)	**≥90 days ($n = 59$)**	***P***
ORR	20 (35%)	29 (49%)	0.12
CBR	26 (46%)	39 (66%)	0.03
	<45 days ($n = 12$)	**≥180 days ($n = 20$)**	
ORR	3 (25%)	11 (55%)	0.09
CBR	3 (25%)	16 (80%)	0.002

≥90-day PFS with ipilimumab had a similar ORR for treatment with pembrolizumab compared with those with <90-day PFS (49% vs. 35%, $P = 0.12$) but a greater CBR (66% vs. 46%, $P = 0.03$; Table 2). The median PFS with pembrolizumab also appeared to be greater in the ≥90-day group (237 vs. 125 days, $P = 0.09$), although this was not statistically significant (Fig. 1A). OS also appeared somewhat higher in the ≥90-day cohort (median OS, 374 vs. 282 days; $P = 0.06$; Fig. 1B).

To assess patients with more extreme phenotypes, we then compared outcomes with pembrolizumab for rapid ipilimumab progressors (PFS < 45 days; $n = 12$) with outcomes from those with prolonged prior ipilimumab benefit (PFS ≥ 180 days; $n = 20$). Patients with prolonged ipilimumab benefit had a seemingly higher ORR (55% vs. 25%, $P = 0.09$) and CBR (80% vs. 25%, $P < 0.01$) with pembrolizumab. Other outcomes were also superior in the prolonged benefit group compared with rapid progressors and all other patients, including PFS (median, 249 vs. 50 vs.176 days; $P = 0.01$) and OS (median, 249 vs. 206 vs. 374 days; $P = 0.03$; Fig. 2A and B). Similar stratification was observed when using other cutoffs to define rapid progression and prolonged benefit, including 60 and 120 days, and dividing patients into tertiles based on PFS (Supplementary Figs. S1 and S2). We also assessed whether prior response to ipilimumab correlated with PFS with pembrolizumab. Although only 7 patients experienced a RECIST-defined response to ipilimumab in this cohort, PFS and OS were ($P = 0.027$ and 0.242, respectively) higher for these patients (Supplementary Fig. S3). Of these 7 patients, 4 experienced a PR or CR with pembrolizumab, and the other 3 had SD (ongoing in 2 patients).

A multivariable ordinal logistic regression model was used to investigate the correlation between ipilimumab PFS with response to pembrolizumab controlled for age, prior therapy, metastatic stage, and LDH. Ipilimumab PFS (measured in months) was independently correlated with subsequent pembrolizumab response (odds ratio, 1.22; $P = 0.04$).

Conclusions

The advent of several effective immune checkpoint inhibitors has markedly improved melanoma outcomes. In this study, we assessed patients who were treated with pembrolizumab after progressing on ipilimumab and found that after accounting for other known prognostic variables, ipilimumab PFS was independently associated with pembrolizumab outcomes. In particular, patients with prolonged benefit from ipilimumab treatment had excellent response rates, PFS, and OS with pembrolizumab. In contrast, patients with rapid progression with ipilimumab tended to have a worse outcome with pembrolizumab. A subset of these patients, however, did show a response and had prolonged benefit. This suggests that "immune-responsive" and "immune-resistant" phenotypes may be shared among distinct therapies.

In view of numerous clinically active immune and targeted therapies, understanding the most effective sequences and

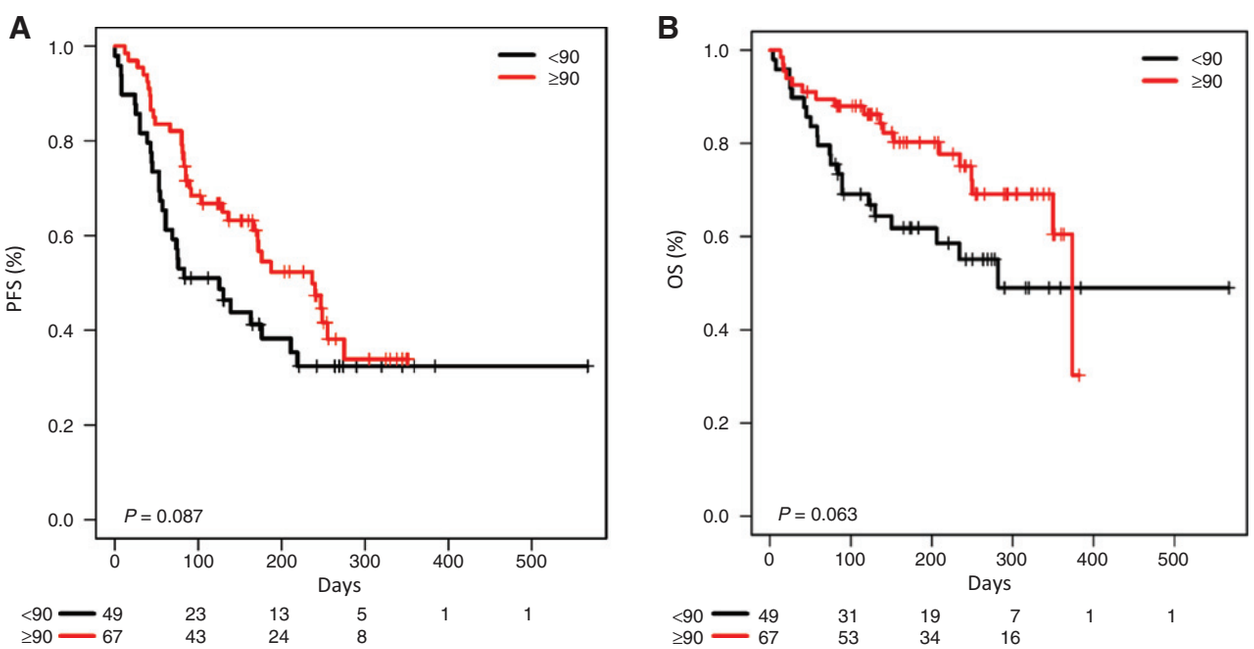

Figure 1.

A, PFS with pembrolizumab in patients with ≥90-day PFS versus patients with <90-day PFS with ipilimumab (237 days vs. 125 days, $P = 0.09$). B, OS with pembrolizumab in patients with ≥90-day PFS versus patients with <90-day PFS with ipilimumab (374 days vs. 282 days, $P = 0.06$).

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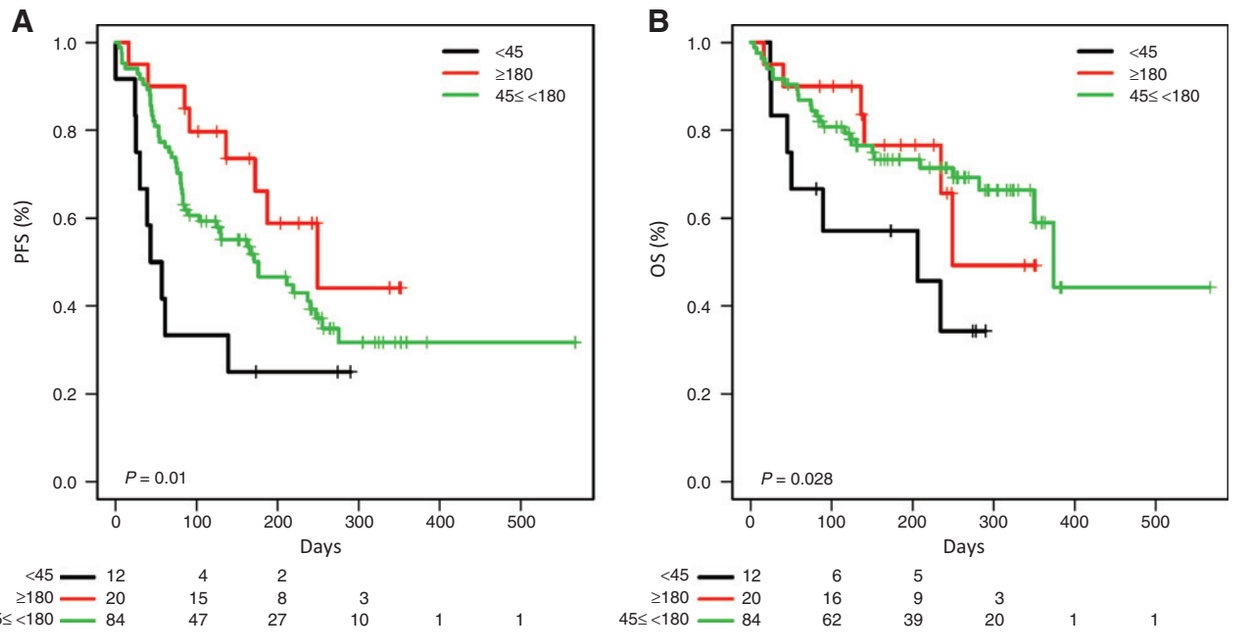

Figure 2.

A, PFS with pembrolizumab based on prolonged benefit (≥180 days), rapid progression (<45 days), and all others on ipilimumab (249 vs. 50 vs. 176 days, $P = 0.01$). B, OS with pembrolizumab based on prolonged benefit (≥ 180 days), rapid progression (<45 days), and all others on ipilimumab (249 vs. 206 vs. 374 days, $P = 0.03$).

combinations is a major priority. Either pembrolizumab or nivolumab as monotherapy, or the combination of ipilimumab and nivolumab, is superior to single-agent ipilimumab (9, 10). A retrospective study by our group and others suggested that ipilimumab could benefit patients who previously progressed on high-dose IL2, regardless of the degree of response or PFS with IL2 (12). Two other retrospective studies have suggested that ipilimumab rarely benefits patients following progression on BRAF inhibitors, but that BRAF inhibitors may be effective after immune therapy failure (13, 14). This study, however, assessed the correlation between ipilimumab and pembrolizumab benefit and revealed a potentially useful association.

Whereas pembrolizumab, nivolumab, or even combined ipilimumab and nivolumab have already become the first-line immune therapy, these data have value for several reasons. First, they suggest that overlap exists between patients who benefit from different immune therapies, implying a shared immune phenotype. Second, our data suggest that prognostic information may be provided for many patients who have been or will be treated with ipilimumab in the first line, either due to prolonged responses or to delays in practice pattern changes. In particular, this information may inform treatment for patients with more durable benefit from ipilimumab who ultimately progress, and provides a possible treatment alternative to ipilimumab re-induction. Third, these data suggest that assessing other treatment sequences is critically important. For example, investigating the outcomes of patients treated with ipilimumab following anti–PD-1 failure will be particularly vital. A prior study has reported that 2 of 12 patients responded to ipilimumab following nivolumab failure (15), although a much larger experience will be needed for any firm conclusions.

This study has several limitations. Patients were treated largely with standard-of-care therapy (off clinical trials) and were therefore subject to nonstandardized timing for tumor assessments by cross-sectional imaging. Second, ipilimumab PFS may be difficult to measure accurately given the occasional atypical, immune-related responses. In this study, we used RECIST 1.1 criteria to standardize PFS calculations. Finally, the follow-up time on pembrolizumab was relatively short, limiting our ability to evaluate prolonged survival data, although differences in outcomes were particularly striking in the first several months on therapy. Despite these limitations, we observed a correlation between ipilimumab PFS and subsequent responses to pembrolizumab.

In conclusion, we observed that the duration of PFS with ipilimumab correlated with subsequent pembrolizumab treatment responses. This study provides useful prognostic information for patients treated with immune therapies and suggests investigation into shared immune features that predict benefit (or lack thereof) from both ipilimumab and pembrolizumab.

Disclosure of Potential Conflicts of Interest

D.B. Johnson is a consultant/advisory board member for Genoptix and Bristol-Myers Squibb. 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.): A. Shreders, R. Joseph, C. Peng, I. Puzanov, J.A. Sosman, D.B. Johnson
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): R. Joseph, F. Ye, S. Zhao, I. Puzanov, D.B. Johnson
Writing, review, and/or revision of the manuscript: A. Shreders, R. Joseph, F. Ye, S. Zhao, I. Puzanov, J.A. Sosman, D.B. Johnson
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): I. Puzanov, J.A. Sosman, D.B. Johnson
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