Priority Brief

Cancer Immunology Research

Clinical Features of Acquired Resistance to Anti–PD-1 Therapy in Advanced Melanoma

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Abstract

Anti–PD-1 therapy has improved clinical outcomes in advanced melanoma, but most patients experience intrinsic resistance. Responding patients can develop acquired resistance to anti–PD-1. We retrospectively reviewed 488 patients treated with anti–PD-1 from three academic centers and identified 36 patients with acquired resistance, defined as disease progression following objective response. The incidence, timing, disease sites, post-progression survival (PPS), and outcomes were evaluated descriptively. The acquired resistance cohort consisted of 67% with more than 1 feature of poor prognosis (stage M1c, elevated LDH, or brain metastasis), and 67% had previously received ipilimumab. Partial and complete responses were achieved in 89% ($n = 32$) and 11% ($n = 4$) of patients, respectively, and median time to resistance (progression-free survival; PFS) was 11.1 months (range 4.3–32.8 months). Most progression was isolated (78% of patients, $n = 28$) and occurred while receiving therapy (78%, $n = 28$). The median PPS was 12.8 months (range 0.1–51.8 months), and the median overall survival was 33.7 months. Among isolated progressors, 15 received localized therapy (12 with surgery, 3 with radiation). Patients with isolated versus systemic progression exhibited a trend for improved PPS ($P = 0.081$), and patients with an initial PFS $\geq$ 15 months showed significant PPS improvement ($P = 0.036$). Two patients experienced subsequent responses to anti–PD-1 resumption. In conclusion, acquired resistance to anti–PD-1 was frequently associated with excellent clinical outcomes and often presented as isolated progression amenable to localized therapy (surgery or radiation) or systemic progression sensitive to therapy resumption. *Cancer Immunol Res; 5(5); 357–62. ©2017 AACR.*

Introduction

Agents blocking the interaction between the checkpoint inhibitor programmed cell death-1 (PD-1) and its ligand (PD-L1) have dramatically improved clinical outcomes for patients with advanced melanoma compared with conventional therapies. Up to 45% of patients receiving anti–PD-1 therapy experience an objective response, and a 34% 5-year survival rate with single-agent anti–PD-1 was reported in a small set of patients (1). Despite these advances, most patients ultimately experience intrinsic (lack of initial response) or acquired (response followed by progression) resistance (2–5). Reliable predictors of resistance have yet to be characterized. However, a number of studies have identified clinical features (elevated lactate dehydrogenase, bulky disease, presence of liver metastases) and molecular correlates (low nonsynonmous mutation load, angiogenesis/wound healing signatures, lack of $CD8^+$ T-cell infiltrate, lack of PD-L1 expression by tumor or inflammatory cells, particular oncogenic pathway activation) of intrinsic resistance (6–16).

Although intrinsic resistance has received the most focus, a modest number of patients clearly develop acquired resistance to anti–PD-1. For example, long-term analysis of phase I trial participants with advanced melanoma treated with nivolumab revealed that nearly half (42%) of responders ultimately experienced disease progression at a median of 24 months (17). Overall, this represented approximately 13% of patients in this clinical trial cohort. Likewise, the phase I study of pembrolizumab revealed a similar percentage (8.1% of total cohort, 24% of responders) of patients who progressed after response (18). Acquired resistance is a familiar limitation of targeted therapy (e.g., inhibitors of mutant BRAF or EGFR) for various cancers, but this concept is less well explored for immune therapies, including anti–PD-1 antibodies. Molecular characterization of acquired anti–PD-1 resistance has been performed on a limited number of samples, and the clinical features of resistance are unexplored.(6, 19)

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We sought to characterize the incidence, timing, and clinical features of acquired resistance to anti–PD-1 therapy in advanced melanoma. We also aimed to assess the post-progression outcomes in this population. To accomplish this, we reviewed the clinical courses of patients at three large academic institutions who received single-agent anti–PD-1 and achieved an objective response with subsequent progression of disease.

Methods

Patients

Following approval from each site's institutional review board (IRB), we screened all patients who received single-agent anti–PD-1 (nivolumab or pembrolizumab) at each participating center ($n = 488$). From these, we identified patients who experienced response followed by progression ($n = 36$). These centers included Dana Farber Cancer Institute ($n = 9$), Moffitt Cancer Center ($n = 12$), and Vanderbilt University Medical Center ($n = 15$). As the data was retrospective, waiver of consent was obtained at all sites. We included patients with unresectable or metastatic melanoma who had received at least one dose of anti–PD-1 therapy and achieved either partial or complete response as measured by Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria (20). Patients treated with combination nivolumab and ipilimumab, or other anti–PD-1–based combinations were not included. Patients were included only if they experienced RECIST-defined disease progression of disease following their initial response.

Study design

We obtained baseline demographic data for each patient including age, gender, American Joint Committee on Cancer (AJCC, 7th ed. 2010) pathologic stage, performance status defined by the Eastern Cooperative Oncology Group (ECOG), and serum lactate dehydrogenase level (LDH). Additional information regarding prior treatments and responses were also recorded. To assess the efficacy of initial anti–PD-1 therapy, we evaluated the objective response based on RECIST v1.1 criteria, progression-free survival (PFS), and overall survival (OS) of patients with acquired resistance. To explore whether increasing PFS would correlate with improved survival after progression, we assessed a range of PFS cut-off points (6, 9, 12, and 15 months; Supplementary Fig. S1). Finally, to characterize post-progression clinical outcomes, we collected data following disease progression including sites of progression, subsequent treatments, treatment responses, and survival. Isolated disease progression was defined as progression in one organ, whereas systemic progression involved >1 organ system. We considered "new" lesions at progression as tumors not present at treatment initiation (even if in the same organ as a preexisting lesion), whereas "existing" lesions were those that responded then progressed.

Statistical analysis

OS and PFS were calculated on the basis of the Kaplan–Meier method. PFS was defined as time from the start of treatment until disease progression. Post-progression survival was defined as time from disease progression until death for any reason. OS was defined as time from the start of treatment until death for any reason. Patients were censored at their last follow-up. Survival was compared between groups using the log-rank test. Continuous and categorical variables were described using means and percentages, respectively. Analyses were performed using the statistical software R version 3.3.0 and GraphPad Prism 7.

Results

Baseline patient characteristics

From a total of 488 patients screened from 3 centers, 166 (34%) responded initially to anti–PD-1 therapy and 36 (7.4%) developed acquired resistance. There was a 21.7% incidence of acquired resistance among responders to anti–PD-1 therapy (21 received pembrolizumab alone, 14 received nivolumab alone, and 1 received nivolumab and vaccine). Patient baseline characteristics are described in Table 1. All subsequent percentages refer to the 36 patients in the acquired resistance cohort unless specified. Of these, 67% were male ($n = 24$) and ages ranged from 31 to 88 with a median of 62. Most patients had melanoma with a cutaneous primary (89%, $n = 32$). Most patients who acquired resistance had received previous treatment (89%, $n = 32$), including 24 patients with prior ipilimumab therapy. Twenty-four patients (67%) had at least one poor prognostic feature including brain metastasis, elevated LDH or stage IV M1c disease. Of the patients with evaluable mutational status, 26% had a *BRAF* mutation and 35% had an *NRAS* mutation. Four (11%) patients with acquired resistance achieved a complete response, while the remainder experienced partial response (Fig. 1). The median follow-up for the cohort was 33.1 months (range 6.1–64.6 months). The Supplementary Fig. S2 provides a radiographic and clinical example of one individual patient who had an initial response with an isolated site of disease progression.

Characteristics at progression

The median PFS (i.e., time to acquired resistance) was 11.1 months (range 4.3–32.8 months; Fig. 2A). Patient progression

Table 1. Patient baseline demographics

Characteristic	No. (%) ($n = 36$)
Age, median (range)	62 (31–88)
Sex	
Male	24 (66.7)
Female	12 (33.3)
Primary site	
Skin	33 (88.9)
Acral	2 (5.6)
Mucosal	1 (2.8)
Unknown	1 (2.8)
Stage	
IV M1a/b	12 (33.3)
IV M1c	24 (66.7)
Brain metastases	9 (25.0)
Elevated LDH	9 (25.0)
Mutational status[a]	
BRAF	8 (25.8)
NRAS	7 (35)
Prior treatment	
BRAF and/or MEK inhibitor	4 (11.1)
CTLA-4 inhibitor	24 (66.7)
None	4 (11.4)
Type of response	
Partial response	32 (88.9)
Complete response	4 (11.1)

[a]Percentage is of evaluable patients

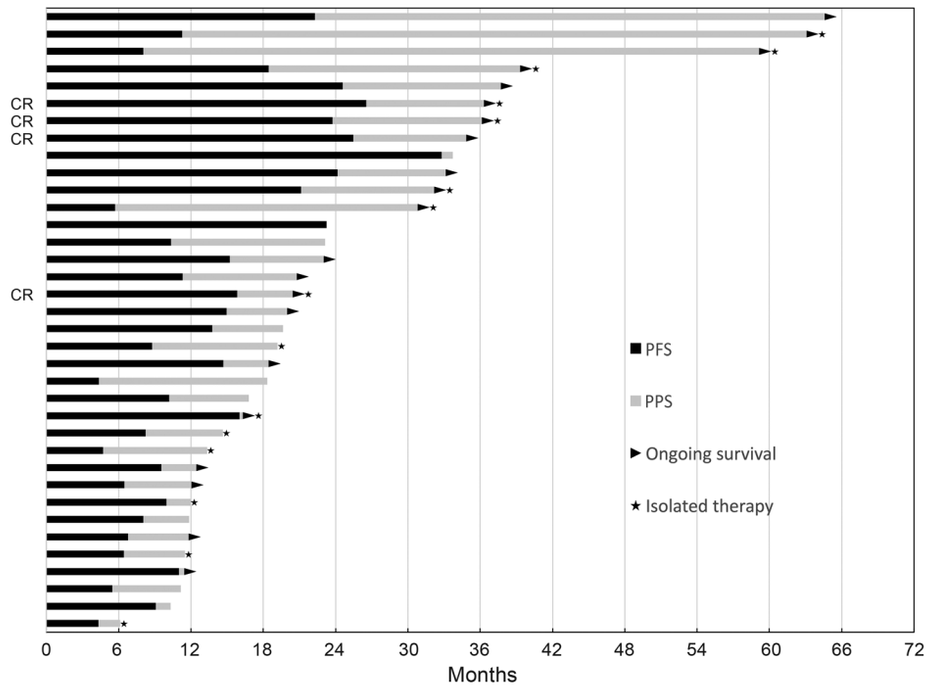

Figure 1.
Swimmer's plot for progression-free and PPS of the patients with acquired resistance. CR, complete response.

characteristics are described in Table 2. The majority of patients had isolated (single organ) sites of progression (78%, $n = 28$), usually with visceral involvement ($n = 18$, 50%), including 4 patients with brain metastases. Other sites of progression were either in lymph nodes ($n = 8$, 22%) or as soft tissue sites ($n = 2$, 6%). Overall, there was a slight preponderance of progression at new site(s) of disease only ($n = 19$, 53%); 14 patients in the acquired resistance cohort (39%) experienced progression at existing site(s) only and 3 patients (8%) had disease progression at both new and existing sites. Most patients were receiving therapy at the time of progression, although 8 (22%) had discontinued therapy for at least 3 months prior to progression.

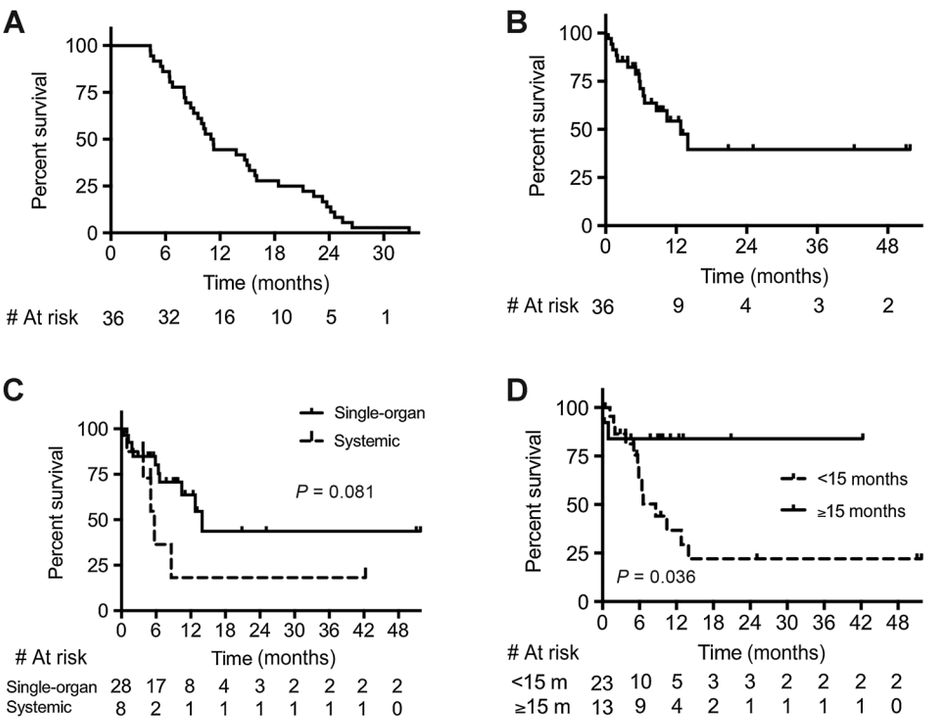

Figure 2.
A, PFS, PPS (**B**) in the acquired resistance cohort, PPS in single-organ versus systemic progression (**C**), and PPS cutoff at 15 months (**D**).

Table 2. Progression characteristics

Characteristic	No. (%) ($n = 36$)
Type of progression	
Systemic	8 (22.2)
Localized	28 (77.8)
Site of progression	
New only	19 (52.8)
Existing only	14 (38.9)
Both	3 (8.3)
Initial treatment at progression	
Surgery	12 (33.3)
Radiation	3 (8.3)
Systemic	15 (41.7)
None/Hospice	5 (13.9)
Undecided	1 (2.8)
Type of systemic therapy after progression	
Anti-PD-1	11 (30.6)
Continued same agent	8 (22.2)
Switched to different agent	3 (8.3)
Anti-CTLA-4	3 (8.3)
Combination PD-1/CTLA-4	1 (2.8)
BRAF and/or MEK inhibitor	5 (13.9)
Clinical trial[a]	4 (11.1)
Chemotherapy	1 (2.8)
Alive	
Yes	21 (58.3)
No	15 (41.7)

[a]Included trials (2) with ERK inhibitor and antibody–drug conjugate.

Post-progression treatments

Following progression in the acquired resistance cohort, 15 patients (42%) received systemic treatment initially, and another 15 (42%) received localized treatments for isolated sites of disease progression (surgery in 12, radiation in 3). Of those that received post-progression systemic therapy ($n = 22$) either immediately following progression or following initial surgery or radiation, 11 patients received anti–PD-1 therapy with 8 patients continuing the same anti–PD-1 agent and 3 patients switching to another anti–PD-1 drug (e.g., pembrolizumab to nivolumab or vice versa). Other types of systemic therapy included BRAF and/or MEK inhibitors ($n = 5$), ipilimumab ($n = 3$), clinical trials ($n = 4$), or chemotherapy ($n = 1$).

Patient outcomes

The median overall survival in the acquired resistance cohort was 33.7 months (Supplementary Fig. S3) with a median post-progression survival (PPS) after disease progression of 12.8 months (Fig. 2B). When comparing the median PPS of patients with isolated (single-organ) versus systemic progression, patients with isolated progression trended toward improved overall survival (median PPS 14.0 months vs. 5.7 months, $P = 0.081$; Fig. 2C). Patients with initial PFS of $\geq$15 months had significantly improved PPS as compared with those with a PFS < 15 months (not reached vs. 8.6 months, $P = 0$ .036; Fig. 2D). Similar trends existed for other PFS cutoffs (Supplementary Fig. S1). The PPSs of patients with *BRAF* or *NRAS* mutation were not different from respective wild-type cohorts.

Eight patients underwent surgery for an isolated site of disease progression with curative intent (goal of "surgical CR"). Of these, 7 have not had any further progression, and only one patient has died, with a median follow up of 36.2 months. Four other patients had surgery for symptomatic disease progression in the presence of systemic or other disseminated disease progression, and all of these patients have died. Regarding systemic therapy, 3 patients received ipilimumab with evaluable responses, including 1 with a subsequent partial response (below). One patient experienced an excellent partial response to dabrafenib and trametinib, one had primary disease progression on dabrafenib, and 3 patients progressed on trametinib (administered in the setting of *NRAS* or non-V600E/K *BRAF* mutations).

A major clinical question currently is the timing of anti–PD-1 cessation, and whether progression following cessation would remain sensitive to therapy. Although most patients progressed while still receiving anti–PD-1, 8 experienced disease progression following cessation of therapy (because of patient preference, completion of clinical trials, or toxicity) for at least 3 months. Of these, 2 patients experienced a subsequent response after resumption of anti–PD-1 therapy, 2 experienced further progressive disease following resumption of anti–PD-1 therapy, and 3 had surgery or radiation to isolated sites of progression without further recurrence or treatment (4.6–12.4 months later). The final patient had an excellent response to ipilimumab that has persisted >3 years.

Four patients (11%) also experienced isolated disease progression in the brain. Of these, one underwent radiation followed by resumption of pembrolizumab (no evaluable response yet), 2 had surgery for a symptomatic brain metastasis (both ultimately died within 6 months later), and one was transitioned to hospice care.

Discussion

Anti–PD-1 agents have clearly transformed treatment paradigms for numerous malignancies, producing durable responses in a sizable fraction of patients. These agents, however, are encumbered both by intrinsic and acquired resistance. With the increasing use of anti–PD-1 agents, characterizing resistance at a clinical and molecular level is particularly critical. In this study, we observed that acquired resistance in advanced melanoma occurred in approximately 22% of patients who respond to anti–PD-1 therapy with a median onset of 11 months after initiation of anti–PD-1 therapy. Therefore, clinical characterization of this defined population provides important prognostic information for patients who progress after initial anti–PD-1 response. In addition, further understanding of post-progression outcomes improves our ability to make appropriate therapeutic choices.

Importantly, we observed that many patients experienced excellent post-progression outcomes. Patients who had isolated disease progression (78%) had improved survival compared with those with systemic progression. Many of these patients received localized therapies (42%) with either surgery or radiation. Thus, there appears to be a frequent clinical pattern of patients with isolated progression that may still experience durable benefit with localized therapy or anti–PD-1 resumption following progression.

At a molecular level, acquired anti–PD-1 resistance could reflect changes in the tumor (loss of responsive tumor antigens or loss of IFNγ/MHC signaling), tumor microenvironment (myeloid-derived suppressor cells, tumor associated macrophages, Tregs), or PD-1 independent mechanisms of immunosuppression (upregulation of other immune checkpoints) (6, 7, 19, 21–25). Molecular studies have begun to shed light on these mechanisms. In melanoma patients with acquired resistance to pembrolizumab, loss-of-function mutations in *JAK1*

and *JAK2* mediated resistance through disrupted IFNγ receptor signaling. Another resistant sample in this study demonstrated a defect in the antigen-presenting protein β_2-microglobulin (β_2M), causing loss of MHC class I heavy chain outer-membrane localization, despite constitutive production, suggesting a defect in antigen presentation (19). In addition, in preclinical mouse models of non–small cell lung cancer with acquired anti–PD-1 resistance, other immune checkpoints, notably TIM-3, can be upregulated in tumor-infiltrating lymphocytes (25). These studies highlight the heterogeneous nature of adaptive resistance, which could potentially reflect the diverse clinical patterns in our study.

Clinical definitions of anti–PD-1 resistance have not been established, and remain an unmet need. For example, resistance to platinum-based chemotherapy has been classified in many tumor types depending on the time of progression (e.g., platinum-refractory vs. platinum-sensitive ovarian cancer), and remain a useful tool for clinical decision-making and trial accrual. Similarly, we speculate that there may be clinical phenotypes of disease progression on anti–PD-1 therapy. On the basis of our data, one could conjecture that "anti–PD-1 sensitive" could be used to define patients who relapse after treatment discontinuation (either in the metastatic or perhaps in the adjuvant setting), or have isolated relapse amenable to local therapy (with continued systemic disease control). In contrast, patients with systemic disease progression while still receiving therapy may have a more aggressive course and could be termed "anti–PD-1 resistant." At this time, these concepts are speculative and large prospective studies are needed to establish more refined and biologically relevant classifications of anti–PD-1 resistance.

This study has several limitations. First, the sample size is relatively small but represents the largest retrospective study of acquired resistance in anti–PD-1 therapy. Furthermore, this represents a concerted effort to evaluate patients from multiple large centers who received anti–PD-1 (488 patients). Second, due to the retrospective nature of this study, the protocols for treatment of localized or systemic progression were not standardized, and were largely driven by physician/patient preference. Third, we could not compare our data to detailed demographic information of responders, who did not experience acquired resistance, as it was not feasible to collect all these data. Finally, some patients had relatively short follow-up times. Despite these limitations, our study begins to characterize acquired resistance to these transformative agents and provides a foundation for future clinical investigations with combination immunotherapy and in other tumor types.

As the use of anti–PD-1 therapy becomes more prevalent, acquired resistance will become a challenging and more common clinical dilemma for oncologists. We observed a predominant clinical pattern of resistance with patients developing isolated disease that is amenable to local therapy or anti–PD-1 resumption with subsequent durable benefit. In the setting of isolated progression, therefore, multidisciplinary management should occur, with strong consideration for surgery or radiation to the single lesion. Furthermore, anti–PD-1 resumption should be considered in patients progressing after cessation of therapy. Ultimately, further studies on larger cohorts will be needed to fully characterize the mechanisms that drive these relapses and their link to clinical outcomes.

Disclosure of Potential Conflicts of Interest

J.J. Luke reports receiving other commercial research support from Bristol-Myers Squibb and Merck and is a consultant/advisory board member for Bristol-Myers Squibb and Merck. R.W. Joseph is a consultant/advisory board member for Bristol-Myers Squibb, Merck, Exilixis, Genoptix, Eisai, and Nektar. P.A. Ott is a consultant/advisory board member for Genentech, BMS, and Pfizer. F.S. Hodi reports receiving a commercial research grant from Bristol-Myers Squibb (to the institution) and is a consultant/advisory board member for Merck, Genentech, Novartis, and EMD Serono. D.B. Johnson reports receiving a commercial research grant from Incyte, is a consultant/advisory board member for Bristol-Myers Squibb and Genoptix. No potential conflicts of interest were disclosed by the other authors.

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Development of methodology: D.Y. Wang
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Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): D.Y. Wang, P.D. Leger, S. Zhao, F. Ye, R.W. Joseph, F.S. Hodi, J. Sosman, D.B. Johnson, E.L. Buchbinder
Writing, review, and/or revision of the manuscript: D.Y. Wang, Z. Eroglu, P.D. Leger, S. Zhao, F. Ye, J.J. Luke, R.W. Joseph, R. Haq, P.A. Ott, F.S. Hodi, J. Sosman, D.B. Johnson, E.L. Buchbinder
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): D.Y. Wang, P.D. Leger, F.S. Hodi
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