Impact of NRAS Mutations for Patients with Advanced Melanoma Treated with Immune Therapies

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Abstract

Activating NRAS mutations are found in 15% to 20% of melanomas. Immune therapies have become a mainstay in advanced melanoma treatment. We sought to evaluate whether tumor genotype (e.g., NRAS mutations) correlates with benefit from immune therapy in melanoma. We identified 229 patients with melanoma treated with immune therapies [IL2, ipilimumab, or anti-programmed cell death-1/ligand-1 (PD-1/PD-L1)] at three centers and compared clinical outcomes following immune therapy for patients with or without NRAS mutations. Of the 229 patients with melanoma, 60 had NRAS mutation, 53 had BRAF mutation, and 116 had NRAS/BRAF wild type. The NRAS-mutant cohort had superior or a trend to superior outcomes compared with the other cohorts in terms of response to first-line immune therapy (28% vs. 16%, P = 0.04), response to any line of immune therapy (32% vs. 20%, P = 0.07), clinical benefit (response + stable disease lasting ≥24 weeks; 50% vs. 31%, P < 0.01), and progression-free survival (median, 4.1 vs. 2.9 months, P = 0.09). Benefit from anti-PD-1/PD-L1 was particularly marked in the NRAS cohort (clinical benefit rate 73% vs. 35%). In an independent group of patient samples, NRAS-mutant melanoma had higher PD-L1 expression (although not statistically significant) compared with other genotypes (6/12 vs. 9/20 samples with ≥1% expression; 6/12 vs. 6/20 samples with ≥5% expression), suggesting a potential mechanism for the clinical results. This retrospective study suggests that NRAS mutations in advanced melanoma correlate with increased benefit from immune-based therapies compared with other genetic subtypes. If confirmed by prospective studies, this may be explained in part by high rates of PD-L1 expression. Cancer Immunol Res. 3(3); 288–95. ©2015 AACR.

Introduction

The advent of molecular genetics has enabled classification of melanoma into clinically relevant subsets defined by the presence of specific “driver” mutations, each with unique clinical and genetic features. These “driver” mutations occur in multiple oncogenes, including BRAF, NRAS, and CKIT, and may serve as potential therapeutic targets. NRAS-mutant melanoma is a distinct cohort of this disease that comprises 15% to 20% of all melanomas and appears to confer a poor prognosis (1, 2). In contrast with BRAF-mutant melanoma, no effective small-molecule inhibitors have been approved that specifically target NRAS, although MEK inhibitors have demonstrated modest clinical activity in a phase II trial (3). In addition, melanomas without driver mutations in BRAF or NRAS (which comprise ~35% of all melanomas—hereafter referred to as “WT” for “wild type”) represent another challenging subgroup without genotype-directed treatments (4, 5). More effective therapeutic strategies both for NRAS-mutant and WT melanomas are urgently needed.

Immune therapies are playing an increasing role in the treatment of patients with metastatic melanoma, particularly when there is no specific targeted therapy available. IL2 was a mainstay of melanoma therapy for many years, resulting in durable remissions in 5% to 10% of patients despite severe acute toxicities (6). More recently, therapeutic approaches aimed at activating antitumor immunity through blockade of immune checkpoints have shown promise. Ipilimumab, a monoclonal antibody directed at cytotoxic T lymphocyte antigen-4 (CTLA-4), demonstrated a survival advantage in metastatic melanoma (7, 8). Newer checkpoint inhibitors targeting the programmed cell death-1/ligand (PD-1/PD-L1) axis [nivolumab, pembrolizumab (MK-3475), MPDL3280A, etc.] have induced durable objective responses in 25% to 50% of...
patients in early trials (9–12). These novel immune-based therapies are better tolerated than IL2, although potentially severe autoimmune side effects still occur in some patients (13). Currently, no validated biomarkers have consistently predicted clinical responses to the immune therapies, although tumor expression of PD-L1 is likely associated with response to PD-1/PD-L1-directed therapies (9, 14). At present, it is unclear whether specific “driver” mutations, such as NRASG12/G13/Q61 mutations, influence immune therapy outcomes. Preclinical studies have recently suggested that specific tumor driver mutations may affect the antitumor immune response through changes in expression of tumor antigens or checkpoint molecules, or production of immune-suppressive cytokines (15–18). In addition, several studies have suggested that although mutations in Braf did not correlate consistently with response rates to immune therapy, NRAS mutations were associated with more frequent responses in patients treated with IL2 (19–21).

While we were assessing the clinical, pathologic, and therapeutic features affected by genotype in our database at Vanderbilt Ingram Cancer Center (VICC), we observed an association between NRAS mutations and response to immune therapy. Based on this finding, we hypothesized that NRAS mutations may affect the clinical outcome of patients with melanoma treated with immune therapies. We further hypothesized that NRAS-mutant melanoma may be associated with increased expression of PD-L1, potentially contributing to its responsiveness to immune therapies. To investigate, we performed a retrospective study reviewing clinical information from patients with melanomas treated at VICC, Memorial Sloan Kettering Cancer Center (MSKCC), and Massachusetts General Hospital (MGH) and assessed PD-L1 expression in an independent cohort of tumor samples. Our primary endpoints were response rate to immune therapy and clinical benefit rate (CBR; defined as response rate plus stable disease for ≥ 24 weeks); secondary endpoints were overall survival (OS), progression-free survival (PFS), and expression of PD-L1.

Patients and Methods

Study population/design

After Institutional Review Board approval was obtained, the electronic medical records were reviewed for patients with advanced melanoma seen at VICC, MSKCC, and MGH. Patients were included if they had biopsy-confirmed advanced melanoma, underwent molecular profiling for Braf and NRAS mutations between July 1, 2010, and October 1, 2012, and were treated with immune therapies. Immune therapies included in this study were limited to high-dose IL2, ipilimumab, anti–PD-1 [nivolumab (BMS-936558) or pembrolizumab (MK-3475)], and anti–PD-L1 (MPDL3280A). Only patients who received ≥1 week of high-dose IL2 or >1 dose of ipilimumab or anti–PD-1/PD-L1 were included. The study population included patients treated with immune therapies between January 1, 2005, and November 1, 2012. Results (OS and PFS) were updated through February 1, 2014. All patients underwent genotyping for “hotspot” mutations in BRAF and NRAS; most patients also underwent “hotspot” testing of other genes (i.e., CKIT, GNAQ, GNA11, MEK1, etc.), although this was not required. Melanomas with mutations identified in genes other than BrafV600 or NRAS were included within the WT group. Our initial comparison was between NRAS-mutant and WT melanomas, although we subsequently collected clinical data from patients with BRAF-mutant melanoma from two centers (VICC and MGH).

Objective tumor responses were retrospectively assessed by the investigators using the RECIST 1.1 criteria as documented in radiographic study reports (PET or CT scans), provider notes, and/or tumor measurement forms (patients on experimental protocols had prospectively evaluated responses; ref. 22). We evaluated whether patients experienced complete or partial response (CR/PR) to first-line immune therapy or to subsequent lines of immune therapy during their clinical course. Clinical benefit (CB) was also assessed, defined as CR, PR, or stable disease for ≥24 weeks. Any patient without a radiographically evaluable response was classified as a nonresponder. Responses to cytotoxic chemotherapy, molecularly targeted therapy, or additional experimental immune therapies were not assessed. All clinical data were obtained and maintained according to Health Insurance Portability and Accountability Act standards.

Genetic analysis

Molecular profiling was performed by SNaPshot analysis (VICC and MGH) and Sequenom (MSKCC) on formalin-fixed paraffin-embedded tissue (FFPE). The SNaPshot process utilizes multiplex PCR, multiplex primer extension, and capillary electrophoresis, and has been extensively validated and described previously (4). The gene profiles performed for this study at VICC, MSKCC, and MGH are listed in Supplementary Tables S1, S2, and S3. Patients without identified mutations in NRAS or BRAF were classified as “WT.”

Immunohistochemistry analysis

Melanoma samples from patients with advanced melanoma naïve to immune checkpoint inhibitor therapy were selected based on genotype (NRAS-mutant, BRAFV600-mutant, WT). Expression of PD-L1 was measured by immunohistochemical testing in FFPE tumor specimens with a rabbit monoclonal antibody (PD-L1, DC10 clone, Cell Signaling) and an assay developed by Dako. The development of this assay has been previously described (12). Unstained slides were sent from VICC to the outside facility where laboratory personnel performed PD-L1 staining. A pathologist blinded to genotype and patient characteristics determined scores for clinical specimens. Samples were defined as positive at two thresholds: (i) if at least 1% or (ii) if at least 5% of tumor cells exhibited membrane PD-L1 staining at any intensity in a section containing at least 100 cells that could be evaluated, as has been previously described (9, 12, 23).

Statistical analysis

All statistical analyses were performed using SAS version 9.2. Comparisons were considered statistically significant for two-sided P values <0.05. Categorical variables were summarized by frequencies in each study group; comparisons between the NRAS and non-NRAS groups (BRAF-mutant and WT) were performed using the Pearson χ² test. The proportions of patients with best response of CR or PR, or stable disease, were compared between the NRAS and non-NRAS cohorts by the Pearson χ² test. Differences in response rates and clinical benefit rates between groups for each individual therapy are displayed descriptively; we chose to avoid P values due to small numbers per group and multiple comparisons. The proportion
of patients with PD-L1 expression ≥1% or ≥5% within NRAS-mutant melanomas was compared with the proportions of those with BRAF-mutant and WT melanomas using the Fisher exact test. PFS was defined as the time from first immune therapy to first progression or death. OS was calculated by date of first immune therapy to date of death for any reason. Patients alive at the last date of follow-up were censored for OS; patients alive and progression free were censored for PFS. PFS and OS distributions were estimated using the method of Kaplan and Meier and compared using the log-rank test.

**Results**

**Demographics**

A total of 229 patients with advanced melanoma were included. Sixty (26%) melanomas harbored NRAS<sup>G12/Q13/Q61</sup>.
mutations, 53 (23%) had BRAF<sup>V600</sup> mutations, and 116 (51%) were WT for NRAS and BRAF by SNaPshot or Sequenom. Patient characteristics are shown in Table 1. The most common mutation identified was NRAS<sup>Q61R</sup> in 28 cases (47%); 85% of NRAS mutations occurred in codon 61. Age, gender, elevated lactate dehydrogenase, and disease stage were not related to NRAS mutation status, although location of primary tumors differed significantly between the NRAS and non-NRAS groups as previously described (5). Among the 53 patients with BRAF<sup>V600</sup> mutations, 16 had received prior BRAF- and/or MEK-directed targeted therapies and 25 received these agents following the failure of first-line immune therapy.

All 229 patients received one or more immune therapy regimens with 55 (24%) receiving a second line of immune therapy and 9 (4%) regimens (only including immune agents). First-line therapy consisted of high-dose IL2 in 25%, ipilimumab in 62%, and anti–PD-1/PD-L1 in 12% (Table 1). For the second-line immune therapy, IL2 was administered in 7% of patients, ipilimumab in 56%, and anti–PD-1/PD-L1 in 36%. Regimen selection did not differ by NRAS mutation status for first- (P = 0.89) or second-line immunotherapy (P = 0.86); the average number of different lines of immune therapy received per patient was 1.17 for the NRAS cohort, 1.22 for the WT cohort, and 1.44 in the BRAF group. Five patients (3 in the WT group and 2 in the NRAS group) received combination ipilimumab and nivolumab (BMS-936558) and were categorized in the anti–PD-1/PD-L1 group for the subgroup analysis. Nine patients (3 in each group) also received ipilimumab in combination with other agents (sorafenib, dacarbazine, fotemustine, GM-CSF, bevacizumab, imiquimod) on experimental protocols; these patients were classified as having received ipilimumab.

**Patient outcomes**

We assessed the association of NRAS mutation and response to therapy. We compared the proportion of patients in each group who experienced a CR or PR with immune therapy at any time during their clinical course (Table 2). In the NRAS group, 19 of 60 patients (32%) had a CR or PR compared with 34 of 169 (20%) in the non-NRAS groups (P = 0.07). We then compared the proportion of patients who achieved clinical benefit; this comparison more strongly favored the NRAS group (50% vs. 30%; P < 0.01).

**Table 2. Response rate and clinical benefit by NRAS status**

<table>
<thead>
<tr>
<th>Best response to any line of immune therapy</th>
<th>NRAS-mutant</th>
<th>BRAF-mutant</th>
<th>WT</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR/PR</td>
<td>n = 60</td>
<td>n = 53</td>
<td>n = 116</td>
<td></td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>19 (32%)</td>
<td>12 (23%)</td>
<td>22 (19%)</td>
<td>0.068</td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>41 (68%)</td>
<td>41 (77%)</td>
<td>94 (88%)</td>
<td></td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>30 (50%)</td>
<td>16 (30%)</td>
<td>34 (29%)</td>
<td>0.004</td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>30 (50%)</td>
<td>37 (70%)</td>
<td>82 (71%)</td>
<td></td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>17 (28%)</td>
<td>8 (15%)</td>
<td>19 (16%)</td>
<td></td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>43 (72%)</td>
<td>45 (85%)</td>
<td>97 (84%)</td>
<td>0.037</td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>27 (45%)</td>
<td>13 (25%)</td>
<td>31 (27%)</td>
<td>0.006</td>
</tr>
<tr>
<td>CR/PR/SD</td>
<td>33 (55%)</td>
<td>40 (73%)</td>
<td>85 (73%)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: PD, progressive disease; SD, stable disease.

*Pearson χ² test P value for NRAS-mutant versus non–NRAS-mutant patients.
analysis, we assessed the outcome for patients who did not experience clinical benefit from immune-based therapies (poor responders) with evaluable follow-up 6 months after the start of therapy. Among NRAS-mutant poor responders, only 46% (13 of 28) were alive at 6 months compared with 67% (78 of 117) of non–NRAS-mutant poor responders. This finding suggests that patients with NRAS-mutant melanoma who do not benefit from immune therapy retain a poor prognosis.

PD-L1 expression

To investigate the potential mechanisms underlying our clinical observation, we selected an independent cohort of 39 archived samples from patients with advanced melanoma (NRAS-mutant = 15, WT = 14, BRAF-mutant = 10). Patients were naïve to systemic therapy in most cases and had not received immune checkpoint inhibitor therapy (see Supplementary Table S4 for prior therapies and clinical characteristics). Seven samples were not evaluable due to low tumor content or excessive pigmentation precluding assessment. Using a 1% cutoff, NRAS-mutant samples appeared to have a non–statistically significant trend toward higher expression of PD-L1 (8 of 12) compared with WT (4 of 11) and BRAF-mutant (5 of 9). Using a cutoff of ≥5% expression of PD-L1, a potentially higher proportion of NRAS-mutant samples were PD-L1–positive (6 of 12), compared with WT (3 of 11) and BRAF-mutant (3 of 9; Fig. 2 and Supplementary Table S4). Differences in PD-L1 expression between the NRAS-mutant cohort and non-NRAS groups were not statistically significant ($P = 0.23$, 1% cutoff; $P = 0.26$, 5% cutoff; Fisher exact test).

**Discussion**

We hypothesized that "driver mutation" status may influence response to immune therapies, specifically examining the cohort of patients with melanoma harboring activating NRAS mutations. Data from our multi-institutional retrospective analysis suggest that patients with NRAS-mutant melanoma experience higher rates of objective response or prolonged stable disease from immune therapy compared with those with BRAF-mutant and NRAS/BRAF WT melanoma. This benefit was particularly notable for the novel immune checkpoint inhibitors (ipilimumab and anti–PD-1/PD-L1). Although only small numbers were treated, the clinical benefit rate was unexpectedly high with anti–PD-1 or anti–PD-L1, occurring in 8 of 11 patients with NRAS-mutant melanoma compared with only 13 of 37 patients in the non–NRAS-mutant cohorts. This finding could have implications for molecular testing and treatment decision making, and it provides early insights into the complex relationship between tumor genetics and the immune response.

In contrast with BRAF-mutant melanoma, no effective molecularly targeted therapeutic strategies have yet been approved for NRAS-mutant or WT melanoma. Immune therapies, therefore, are the cornerstones of therapy for these subtypes. A recent study by Joseph and colleagues (19) showed that IL2 treatment provided superior efficacy for patients with NRAS-mutant compared with BRAF/NRAS WT melanoma (ORR of 47% vs. 15%), although this analysis included only 15 patients with NRAS-mutant melanoma. Our study is much larger and extends to the non–NRAS-mutant cohorts. It should be noted that although several clinical endpoints strongly favored the NRAS population (ORR to first-line therapy, CBR to any and first-line therapy), only a trend was observed for several others (ORR to any therapy, PFS, OS).

We identified a potential partial explanation for this clinical observation. Because previous studies have shown that PD-L1 expression correlates with response to anti–PD-1, we hypothesized that PD-L1 may be differentially expressed in NRAS-mutant melanoma. We attempted to answer this question using a relatively small, separate cohort of samples from patients who were naïve to treatment with immune checkpoint inhibitors. We observed that PD-L1 expression appeared to be modestly higher in NRAS-mutant–resected tumor samples compared with BRAF-mutant or WT melanoma. This result did not reach statistical significance and needs additional confirmation.

Of interest, a recent study demonstrated that PD-L1 expression did not differ between genotypes in melanoma cell lines (26), suggesting that mutant NRAS does not induce constitutive
expression of PD-L1 but may be associated with enhanced immunogenicity in vivo. One potential hypothesis is that NRAS mutations may occur in melanomas with higher mutational burden, a factor linked with higher response rates to immune therapy (27, 28). Results from a large next-generation sequencing study showed that although not universally elevated, the total mutational burden appeared to be higher in NRAS-mutant melanoma than in melanomas of other subtypes (29). Profiling in larger populations of total somatic mutational burden, mutationally generated neoepitopes, tumor-infiltrating lymphocytes, and melanoma lineage antigens is needed to provide additional insight. Understanding the link between NRAS mutations and other genetic alterations in melanoma with the antitumor immune response may also provide a better rationale for approaching combination strategies of molecularly targeted and immune-based therapy. In addition, PD-L1 expression in melanoma and other cancers has been linked to poor prognosis, although this remains controversial (30–34). Based on our observation, it could be speculated that elevated PD-L1 expression may contribute both to the inferior prognosis of NRAS-mutant melanoma and improved response rates to anti–PD-1.

We observed only a trend toward improvements in OS and PFS in our study. Because previous studies have indicated that unselected patients with NRAS mutations have an inferior overall prognosis, we hypothesized that rapid progression and death in nonresponding patients may explain this finding (1, 2). This was supported by our observation that “poor responding” patients in the NRAS cohort (patients without clinical benefit from immune-based therapies) tended to have rapid disease progression and death. Presumably, the lack of approved molecularly targeted agents and aggressive natural history of NRAS-mutant melanoma has a negative impact on survival. This analysis was exploratory only; the influence of NRAS mutations on OS will need additional follow-up in larger cohorts treated with immune therapy.

Figure 2. Immunohistochemical analysis of tumor cell-surface expression of PD-L1 from representative samples (×20). A, NRAS-mutant melanoma sample with strongly positive expression (>50% of cells). B, WT melanoma with <1% of cells with PD-L1 expression. C, distribution of PD-L1 staining by genotype. D, number of samples evaluated by genotype and whether they were positive for PD-L1 expression (>5%) or negative (<5%).

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population of BRAF/MEK inhibitor pretreated patients could adversely influence clinical outcomes compared with the NRAS and WT cohorts. Conversely, the availability of these therapies upon immune therapy progression may actually skew OS in favor of the BRAF-mutant group, because no such therapies were available to the other subgroups. The low patient numbers and variable pretreatment, therefore, limit the conclusions for the BRAF-mutant cohort, and additional study is needed to define the activity of immune therapy for this genetic subtype.

Our study has several other limitations. Patients identified for this study had received several different immune therapies at three centers across the United States spanning a period of approximately 8 years. In addition, genotyping for BRAF and especially for NRAS mutations was not widely available before 2010; therefore, for patients treated before that time, analysis was largely limited to those surviving to obtain genotyping. Genotyping was also performed with three different assays that could also introduce heterogeneity, although each platform has been extensively validated. In addition, somewhat distinct results were identified between immune therapies (no difference with IL2, more clinical benefit with ipilimumab, and higher responses with anti–PD-1/PD-L1); this may reflect divergent interactions of mutant NRAS with the immune response or may be a consequence of small sample size in each group. Finally, there was heterogeneity in the manner that responses to immune therapies were monitored, as some patients were enrolled in clinical trials and others were receiving treatment as standard of care. Therefore, prospective studies will be needed to confirm our observations.

In conclusion, we suggest that immune therapies, particularly immune checkpoint inhibitors, may be particularly effective treatment options for NRAS-mutant melanoma, a challenging cohort of patients with a poor prognosis. Mechanistic support for this assertion is suggested by high levels of PD-L1 expression in NRAS-mutant melanoma in a small cohort (although no statistically significant difference was noted). Prospective analyses and further mechanistic studies are needed to validate this finding. We are hopeful that these types of studies bring us a step closer to the goal of identifying predictive markers for immune therapy.

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C.M. Lovly reports receiving commercial research grants from AstraZeneca and Novartis. A.J. Iafrate has ownership interest (including patents) in ArcherDx and is a consultant/advisory board member for Bioreference Labs. No potential conflicts of interest were disclosed by the other authors.

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