Cutaneous adverse effects of immune checkpoint inhibitors: Correlating clinical findings with pathology

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DISCLOSURE OF RELATIONSHIPS WITH INDUSTRY

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F030 – Caring for the Cancer Patient: Updates in Cutaneous Oncology and Oncodermatology

DISCLOSURES

[List companies, relevant relationships, compensation]
Here’s a Look at Keytruda, the Drug Jimmy Carter Says Made His Tumors Vanish

by MAGGIE FOX

Jimmy Carter credits the new cancer drug Keytruda for shrinking his brain tumors completely. It’s one more possible victory for the newest class of cancer drugs that empower the immune system to fight off tumors.

But cancer experts note that it’s not at all clear that the drug itself is what shrunk Carter’s tumors. The former president was also treated with radiation to his brain and had a large tumor on his liver removed.

While most immune therapy drugs boost the immune system so that it can battle the cancer, Keytruda was the first drug to take a different approach that disrupts a trick tumors use to hide from immune cells.
CTLA-4 inhibitor: ipilimumab

- Cytotoxic T-lymphocyte antigen-4 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit CTLA-4, which is a negative regulator of T-cell activation

Kandalaft et al., JCO 2011
PD-1 inhibitors: pembrolizumab and nivolumab

- Programmed cell death-1 antibodies
  - Enhances immune response/antitumor activity
  - Inhibit PD-1, which plays an important role in downregulating the immune system by preventing the activation of T-cells, which in turn reduces autoimmunity and promotes self-tolerance

Kandalaft et al., JCO 2011
FDA grants regular approval to nivolumab for adjuvant treatment of melanoma

On December 20, 2017, the Food and Drug Administration granted regular approval to the anti-PD1 monoclonal antibody, nivolumab (OPDIVO, Bristol Myers Squibb Company) for the adjuvant treatment of patients with melanoma with involvement of lymph nodes or in patients with metastatic disease who have undergone complete resection. Nivolumab was previously approved for the treatment of patients with unresectable or metastatic melanoma.

Approval was based on improvement in recurrence-free survival (RFS) in a randomized, double-blind trial, CHECKMATE-238 (NCT02388906), in 906 patients with completely resected, Stage IIIIB/C or Stage IV (AJCC 7th ed) melanoma. Patients were randomly allocated (1:1) to receive nivolumab 3 mg/kg every 2 weeks or ipilimumab 10 mg/kg every 3 weeks for 4 doses then every 12 weeks beginning at Week 24 for up to 1 year. Enrollment required complete resection of melanoma with margins negative for disease within 12 weeks prior to...
Adjuvant Melanoma Therapy — Head-Spinning Progress

Lynn M. Schuchter, M.D.

Every year in the United States, approximately 87,000 patients receive the diagnosis of melanoma. Although most of these patients are cured with simple excision, those with node-positive, stage III melanoma are at increased risk for distant metastasis and death. To date, the Food and Drug Administration (FDA) has approved three adjuvant therapies for such patients, all of which are immunotherapies: high-dose interferon alfa-2b, pegylated interferon alfa, and high-dose nated melanoma has increased from 9 months before 2011 to 2 years or more.

The next logical step was to evaluate these drugs as adjuvant treatments. Long et al.⁴ present the initial results of the COMBI-AD trial involving patients with resected stage III melanoma with BRAF V600E or V600K mutations. In this phase 3 trial, 870 patients were randomly assigned to receive daily oral dabrafenib (a BRAF inhibitor) and trametinib (a MEK inhibitor) or...
Checkpoint inhibitor skin reactions

- Morbilliform eruptions
- Pruritus
- Vitiligo
- Disappearance of pigmented lesions
- Lichenoid dermatitis and mucositis
- Lupus-like reactions
- Bullous pemphigoid and other autoimmune blistering diseases
- Granulomatous reactions
- Erythema multiforme and SJS/TEN-like reactions
- Alopecia areata
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PD-1 inhibitor associated bullous pemphigoid

Mochel et al., JCP 2016
PD-1 inhibitor associated bullous pemphigoid
PD-1 inhibitor associated bullous pemphigoid

- BP ELISA testing positive in both patients
Ipilimumab-related dermatitis herpetiformis

- 27 year old woman with Stage III melanoma, received adjuvant ipilimumab
- Developed asymptomatic pink papules near the elbows, back, buttocks 1 month after starting ipilimumab
Ipilimumab-related dermatitis herpetiformis

Mochel et al., J Cutaneous Path 2016
PD-1 inhibitor-associated lichenoid reactions
Figure 1. Cutaneous Eruptions Consisting of Erythematous Papules With Scale Due to Anti-Programmed Cell Death 1 and Anti-Programmed Cell Death Ligand 1 Therapy

A. Small number of discrete scaly papules on the chest (patient number 4).
B. Hypertrophic scaly papules and plaques on the lower extremity (patient number 10).
C. Inflammation around seborrheic keratoses, in addition to new-onset scaly papules, on the back (patient number 14).
D. Coalescent pseudovesiculated papules on the palm (patient number 6).
E. Scaly, discrete papules and plaques on the palm (patient number 19).
F. Numerous erosions on the penis, resembling erosive lichen planus (patient number 10).

Figure 2. Photomicrographs Showing Lichenoid Interface Dermatitis

A. H&E, ×4
B. H&E, ×10
C. CD3-positive
D. CD8-positive
E. CD4-positive
F. CD3-positive

A-C. Hematoxylin-eosin (H&E) staining, original magnification ×4, ×10, and ×20, respectively. Staining of lymphocytic infiltrate revealed the following immunophenotype: D, CD3-positive (both intraepidermal and intraepithelial lymphocytes), E, CD4-positive (intraepidermal lymphocytes), F, CD8-positive (intraepithelial lymphocytes), and G, CD20 negative.
PD-1 inhibitor infusion site sarcoidosis
Lupus-like cutaneous reaction to PD-1 inhibitor
How does discontinuation of immunotherapy affect melanoma outcomes?

Efficacy and Safety Outcomes in Patients With Advanced Melanoma Who Discontinued Treatment With Nivolumab and Ipilimumab Because of Adverse Events: A Pooled Analysis of Randomized Phase II and III Trials


ABSTRACT

Purpose
Approximately 40% of patients with advanced melanoma who received nivolumab combined with ipilimumab in clinical trials discontinued treatment because of adverse events (AEs). We conducted a retrospective analysis to assess the efficacy and safety of nivolumab plus ipilimumab in patients who discontinued treatment because of AEs.

Methods
Data were pooled from phase II and III trials of patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg every 3 weeks for 4 doses, followed by nivolumab monotherapy 3 mg/kg every 2 weeks (N = 408). Efficacy was assessed in all randomized assigned patients who discontinued because of AEs during the induction phase in N = 98 and in those who did not discontinue because of AEs (N = 233). Safety was assessed in treated patients who discontinued because of AEs (N = 170) at any time and in those who did not discontinue because of AEs (N = 231).

Results
At a minimum follow-up of 18 months, median progression-free survival was 8.4 months for patients who discontinued treatment because of AEs during the induction phase and 10.6 months for patients who did not discontinue because of AEs (P = .971). Median overall survival had not been reached in either group (P = .23). The objective response rate was 58.3% for patients who discontinued because of AEs during the induction phase and 50.2% for patients who did not discontinue. The vast majority of grade 3 or 4 AEs occurred during the induction phase, with most resolving after appropriate management.

Conclusion
Efficacy outcomes were similar between patients who discontinued nivolumab plus ipilimumab treatment because of AEs during the induction phase and those who did not discontinue because of AEs. Therefore, even after discontinuation, many patients may continue to derive benefit from combination therapy.

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Durable Complete Response After Discontinuation of Pembrolizumab in Patients With Metastatic Melanoma


ABSTRACT

Purpose
Pembrolizumab provides durable antitumor activity in metastatic melanoma, including complete response (CR) in about 15% of patients. Data are limited on potential predictors of CR and patient disposition after pembrolizumab discontinuation after CR. We describe baseline characteristics and long-term follow-up in patients who experienced CR with pembrolizumab in the KEYNOTE-001 study (ClinicalTrials.gov identifier: NCT01719867). Patients and Methods
Patients with pembrolizumab-naive or -treated advanced metastatic melanoma received one of three dose regimens of pembrolizumab. Eligible patients who received pembrolizumab for ≥8 months and at least two treatments beyond confirmed CR could discontinue therapy. Response was assessed every 12 weeks by central Response Evaluation Criteria in Solid Tumors version 1.1. For this analysis, CR was defined per investigator assessment, immune-related response criteria, and potential predictors of CR were evaluated using univariate and multivariate analyses.

Results
Of 955 treated patients, 106 (11.0%) achieved CR after median follow-up of 43 months. At data cutoff, 92 patients (97.6%) had CR, with median follow-up of 30 months from first CR. Fourteen (13.3%) patients continued to receive treatment for a median of 40 months. Pembrolizumab was discontinued by 91 patients (95.7%), including 67 (63.6%) who proceeded to observation without additional immunotheraphy. The 24-month disease-free survival rate from time of CR was 88.9% in all 106 patients with CR and 89.9% in the 71 patients who discontinued pembrolizumab after CR for observation. Tumor size and programmed death-ligand 1 status were among the baseline factors independently associated with CR by univariate analysis.

Conclusion
Patients with metastatic melanoma can have durable complete remission after discontinuation of pembrolizumab, and the low incidence of relapse after median follow-up of approximately 2 years from discontinuation provides hope for a cure for some patients. The mechanisms underlying durable CR require further investigation.

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Bullous erythema multiforme

Wang et al., JAMA Derm 2018
Bullous erythema multiforme

- Patient had a markedly delayed onset of cutaneous reaction attributable to pembrolizumab (38 months)
- Developed painful papules, plaques, and bullae on hands, and several oral mucosal erosions
- Resolved with course of prednisone but recurred with next cycle of pembrolizumab given
Delayed cutaneous adverse reactions to PD-1 inhibitors are frequently observed.
Cutaneous adverse reactions may also occur after PD-1 inhibitor therapy has been discontinued.
Alopecia areata in the setting of PD-1 / IDO inhibition
Alopecia areata in the setting of PD-1 / IDO inhibition
Alopecia areata induced by immune checkpoint inhibitors

Zarbo et al., BJD 2017
Checkpoint inhibitor skin reactions

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Thank you!

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