

Kinetics of Response to Ipilimumab (MDX-010) in Patients With Stage III/IV Melanoma

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Summary

Background

- Ipilimumab, a fully human monoclonal antibody that blocks cytotoxic T-lymphocyte antigen-4 (CTLA-4), enhances immune responses to tumor-associated antigens and can result in durable objective responses
- Results from previous studies showed that responses to ipilimumab occurred at various time points—within the first few weeks to several weeks/months post-treatment. The variable time to response is likely due to inter-patient immune system variations and is consistent with the fact that antitumor immune responses require time to generate
- The timing of such responses to ipilimumab are different from those observed with chemotherapy

- The current analysis was undertaken to determine the kinetics of response to ipilimumab and determine the appropriate initial response assessment point

Methods

- Six completed studies in 356 treated patients with stage III/IV melanoma evaluating a variety of dosages, dose schedules and concomitant therapies were reviewed to determine the kinetics and duration of response to ipilimumab treatment
- Ipilimumab was used alone (n=209) or in combination with dacarbazine (n=35), IL-2 (n=36), or gp100 peptide vaccine (n=76). Ipilimumab doses ranged from 0.1 to 20 mg/kg (single or multiple doses)
- Complete and partial response, and stable and progressive disease were evaluated; the majority of patients treated with multiple doses of ipilimumab were initially evaluated for

efficacy at Week 12

Results

- Forty-six patients experienced objective response. Responses occurred after 12 weeks of treatment in 28/46 patients
- Duration of response ranged from 2+ to 60+ months. Response is ongoing in 25 patients; several patients have responses that have been ongoing for years
- Sixteen patients had stable disease (SD) prior to response with durations ranging from 2 to 16 months
- Fifty-six/268 patients from 5 of the studies had SD as their best overall response; the median duration of SD was 15.4+ weeks (range 2+ to 60+ weeks). SD is ongoing in 29 patients
- Four patients had apparent progressive disease prior to response

Conclusions

- Ipilimumab has a novel immunotherapeutic mechanism of action that may take time to induce a response.
- These data suggest that patients should be treated with ipilimumab at least until Week 12, even in the presence of early progressive disease, without the addition of other therapies
- The time course and durability of responses noted with ipilimumab are not traditionally observed with chemotherapeutic regimens
- Immunotherapy with ipilimumab may require redefined measures of efficacy; using Response Evaluation Criteria in Solid Tumors (RECIST) may result in an underestimation of response and clinical benefit

Introduction

- Reversing cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitory signals with ipilimumab, a fully human antagonistic anti-CTLA-4 monoclonal antibody, is a targeted approach to enhancing antitumor T-cell responses¹
- Objective responses (OR), including durable responses, and stable disease (SD) have been observed with ipilimumab mono- or combination therapy in patients with metastatic melanoma²⁻⁷
- The most common adverse events are immune-related (irAEs) and include rash and diarrhea.^{2-6,8} irAEs are usually medically manageable, reversible, and without sequelae
- Responses within the first few weeks of ipilimumab treatment, as well as responses that required weeks/months to develop, have been observed.²⁻⁸ The later responses are consistent with the mechanism of action of the drug and with the time required for the immune system to generate an antitumor response
- As ipilimumab has a novel mechanism of action, different from that of chemotherapy and other immunotherapies, that may require time to induce a response, the current analysis was undertaken to examine the kinetics of response to ipilimumab

Objectives

- Primary: examine the kinetics of response to ipilimumab administration
- Secondary: determine the duration of OR and SD

Patients and Methods

- Preliminary data from 6 completed studies of IV ipilimumab in patients (all were previously treated, with the exception of Study 3 in which patients were chemotherapy naïve) with stage III unresectable or stage IV malignant melanoma were pooled
- The first efficacy assessment in the majority of patients treated with multiple doses of ipilimumab was Week 12 post-treatment initiation

- Study 1: single 3 mg/kg ipilimumab dose
- Study 2: 2 cohorts – 1) 3 mg/kg ipilimumab + gp100 210M/288V peptides (1 mg each) every 3 weeks; 2) 3 mg/kg (single dose) ipilimumab + gp100 peptides followed by 1 mg/kg ipilimumab + gp100 peptides every 3 weeks
- Study 3: 3 mg/kg ipilimumab every 28 days × 4 doses ± dacarbazine (250 mg/m² for 5 consecutive days, every 28 days)
- Study 4: escalating doses (0.1 to 3 mg/kg) of ipilimumab (every 3 weeks) + fixed-dose IL-2 (720,000 U, IV)
- Study 5: escalating intra-patient doses (3 to 9 mg/kg) of ipilimumab ± gp100 210M/288V peptides (1 mg each) every 3 weeks
- Study 6: 3 cohorts – 1) escalating single doses of 2.8/3 and 5 mg/kg ipilimumab on Days 1, 57, and 85; 2) escalating single doses of 7.5, 10, 15, and 20 mg/kg ipilimumab; 3) 10 mg/kg ipilimumab on Days 1, 22, 43, and 64

Results

Patients and Objective Responses

- In total, 356 patients were treated across all 6 studies to date
 - Study 1: n=17
 - Study 2: n=56
 - Study 3: n=72
 - Study 4: n=36
 - Study 5: n=88
 - Study 6: n=87
- 46 patients had a confirmed OR at analysis
 - 11 patients had a complete response (CR) and 35 patients had a partial response (PR) as their best overall response (BOR)
 - 10 patients had a PR that developed into a CR; the median duration of PR prior to CR was 83.5 days (range 39 to 131 days), while the median duration of a CR was 311 days (range 135 to 744 days)
- Of the 46 patients who had an OR, 19 were treated with ipilimumab monotherapy and 27 ipilimumab combination therapy
- 28/46 responders (60.9%) responded at ≥12 weeks of treatment
- ORs observed ≥12 weeks of treatment occurred irrespective of dose, regimen and combination

Stable Disease

- 16 patients experienced SD prior to OR
- 14 patients had SD→PR (including 2 patients who had early progressive disease [PD])
- 2 patients had SD→PR→CR
- Figures 1A and 1B show the kinetics of response of an ipilimumab-treated patient with SD prior to a durable PR
- 56/268 patients from 5 of the studies (Study 5 data not yet available) had SD as their BOR

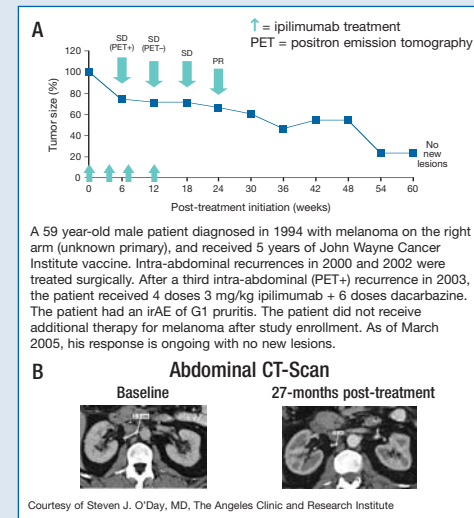


Figure 1. SD prior to PR

Apparent Progressive Disease Prior to Response

- Apparent PD preceded OR in 4 patients
- Subsequent OR occurred without additional treatment with non-study therapies
- Figures 2A and 2B illustrate the kinetics of response in a patient who experienced apparent PD prior to a durable CR

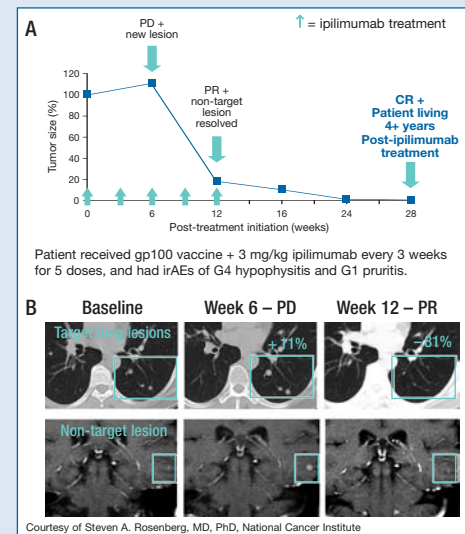


Figure 2. Apparent PD prior to a durable CR

Discussion and Conclusions

- Ipilimumab has a novel immunotherapeutic mechanism of action, that may take time to induce a response
- Responses to ipilimumab may take weeks (≥12 weeks) or months to develop; this is consistent with the mechanism of action of ipilimumab and the time required to mount an antitumor immune response
- Ipilimumab-mediated ORs and SD are durable, lasting months and even years in some patients
- The kinetics and duration of response to ipilimumab are traditionally not observed with chemotherapeutic regimens

Clinical Implications

- These data suggest that, in the absence of rapid disease progression, patients should continue to receive ipilimumab without other therapies until at least Week 12; this will allow time for an antitumor immune response to develop
- Week 12 is now the first assessment point in ongoing ipilimumab clinical trials
- New measures of efficacy are needed; using Response Evaluation Criteria in Solid Tumors (RECIST) may result in missed antitumor responses and, subsequently, reduced clinical benefit

Duration of Response/Stable Disease

- Duration of OR ranged from 2+ to 60+ months; ORs are ongoing in 25 patients (Figure 3)

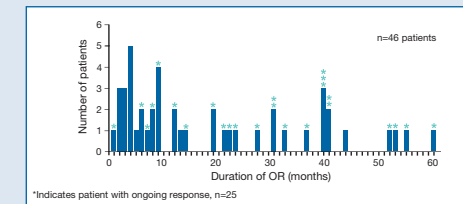


Figure 3. Duration of OR

- The median duration of SD prior to PR was 5.9 months (range 2 to 16 months; includes 2 patients with early PD) (Figure 4)

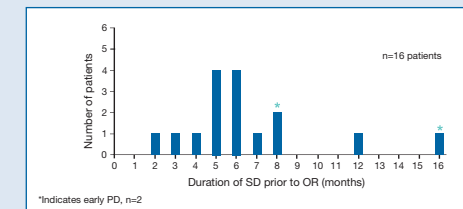


Figure 4. Duration of SD prior to OR

- The median duration of SD as BOR (from 5 studies; Study 5 data not yet available) was 15.4+ weeks (range 2+ to 60+ weeks); 29/56 patients had ongoing SD at the time of analysis (Figure 5)

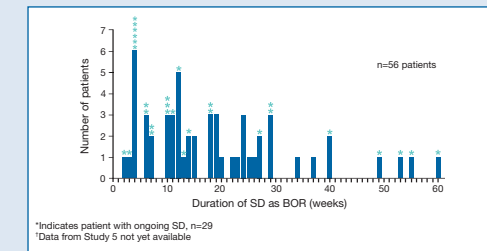


Figure 5. Duration of SD as BOR (5 studies)[†]

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