Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 2010;363:711-23. DOI: 10.1056/NEJMoa1003466.

Supplementary Appendix

Patient Eligibility

Patients with SD of ≥ 3 months duration, from week 12, or who achieved a CR or PR at week 12, were eligible for reinduction if they had an ECOG performance status of 0 or 1. Patients were ineligible for reinduction if they had experienced certain grade 3 or higher immune-related adverse events (e.g., colitis or hepatitis), had active, untreated CNS metastases, or were pregnant or nursing. Patients with PD who were not eligible for continued induction therapy, or for reinduction, were followed for survival status by telephone every 3 months and were permitted to receive non-study anti-cancer therapy at the discretion of the investigator.

Concomitant Medications

Prior medications were defined as any medication taken within 6 weeks of study drug administration and during the study. Concomitant medications were defined as any medication taken during the course of the study. Patients could not use chemotherapy, biochemotherapy, or immunotherapy, have surgery, or receive radiation within 28 days of the first dose of study drug and gamma knife treatment within 14 days of the first dose of study drug. Patients could not use any of the following therapies during the course of the study: IL-2, interferon or other non-study anti-melanoma immunotherapy regimens; cytotoxic chemotherapy; immunosuppressive agents; other investigational therapies; or chronic use of systemic corticosteroids. However, patients with progressive disease who were not eligible for continued therapy or for re-induction were permitted to receive non-study anti-melanoma medications at the discretion of the investigator.

Any concomitant medication was used by 369 of 380 patients (97.1%) in the ipilimumab plus gp100 group, 130 of 131 patients (99.2%) in the ipilimumab-alone group, and 126 of 132 patients (95.5%) in the gp100-alone group. The most common of these were analgesics

(e.g., paracetamol, morphine sulphate, fentanyl, oxycodone, and oxycocet), which were used by more than 70% of patients in each of the three treatment groups. Among other commonly reported concomitant medications, antiemetics and antinauseants (ondansetron hydrochloride, prochlorperazine maleate) and drugs for acid-related disorders (omeprazole, pantoprazole, esomeprazole magnesium) were used by a similar proportion of patients across treatment groups. Antibacterials (ciprofloxacin), antihistamines (diphenhydramine hydrochloride), corticosteroids (prednisone), and antidiarrheals (loperamide) were used by a greater proportion of patients in the ipilimumab treatment groups.

Management of Immune-related Adverse Events

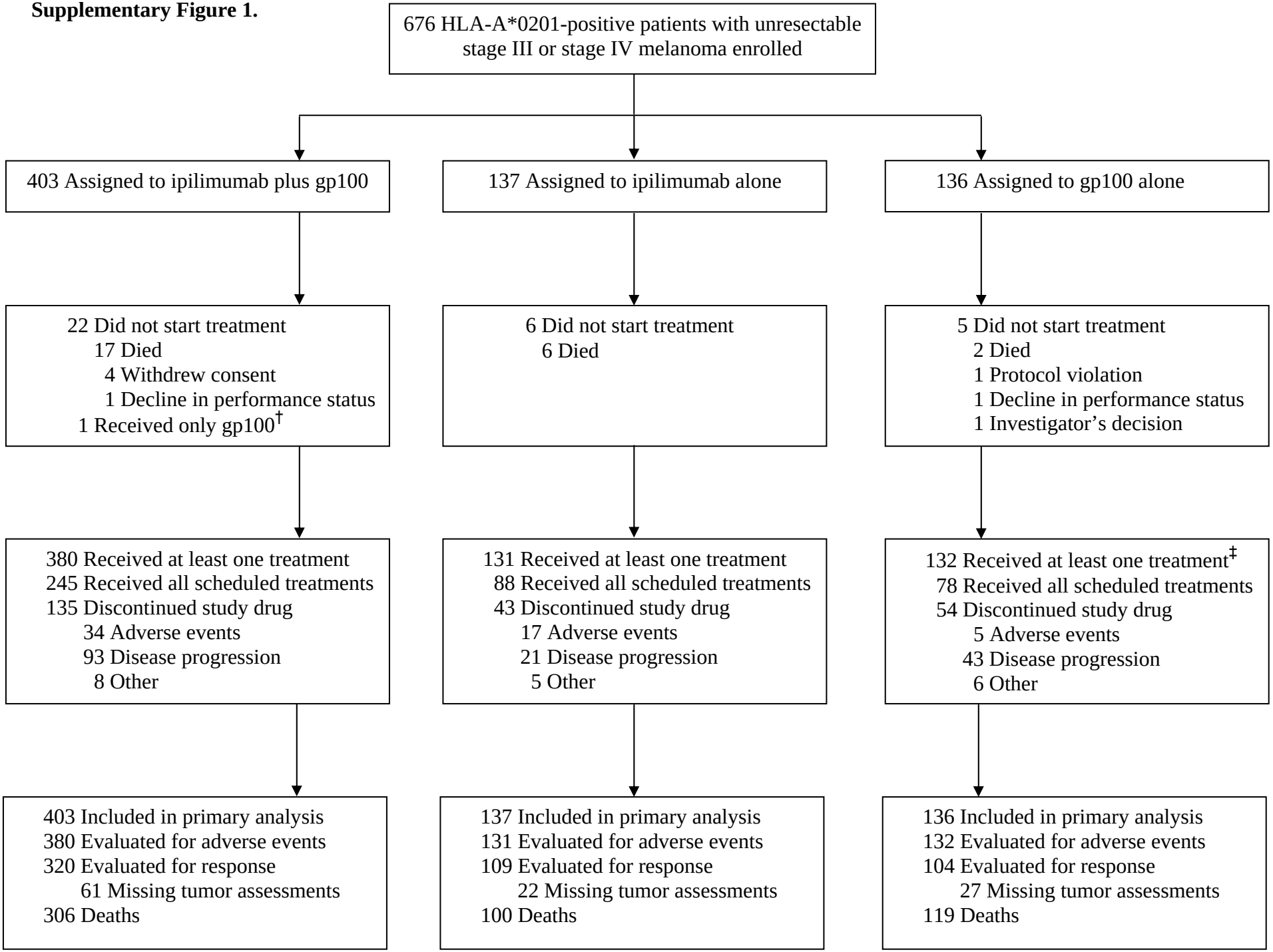
A total of 37 patients (25 in the combination group, 11 in the ipilimumab-alone group, and 1 in the gp100-alone group) were identified who had at least one gastrointestinal immune-related adverse event of grade ≥3 severity. Eight patients (4 in the combination group, 1 in the ipilimumab-alone and 3 in the gp100-alone group) were identified who had at least one hepatic immune-related adverse event of grade ≥3 severity. Among those with gastrointestinal immune-related adverse events, the majority (approximately 75%) received systemic corticosteroids either shortly before or within 10 days of onset; approximately 15% received the steroids >10 days after the event onset; and approximately 10% (4 patients) were never treated with systemic steroids. Overall, 4 patients had an alternate immunosuppressive (all infliximab) added to the steroid regimen in order to manage the gastrointestinal event. With respect to alternate immunosuppression, one patient received intravenous IgG and subsequently cyclosporine for the treatment of a grade 3 immune-related adverse event of hemolytic anemia, which started approximately 3 weeks after the initiation of study therapy with ipilimumab plus gp100.

The frequency of hepatic immune-related adverse events of grade ≥3 severity was lower, with only 8 patients identified (4 in the combination group, 1 in the ipilimumab-alone group,

and 3 in the gp100-alone group). These 3 hepatic events account for 3 out of a total of 5 events reported among 5 gp100 patients having grade ≥3 immune-related adverse events (1 patient with an increased amylase level as well as an LFT elevation, and 1 patient with diarrhea). The rate of steroid treatment was lower than for gastrointestinal events, with only 3 of the 8 receiving systemic steroids (all within 10 days of onset). Among these 8 patients, 4 had known liver metastases at baseline, which may have complicated the decision-making regarding the use of steroids for the hepatitis event.

Supplemental Figure 1: Enrollment, Randomization, and Follow-up of Patients in the Study (CONSORT Flow Chart).

Supplementary Figure 1.



†This patient was included in the gp100-alone group for safety analyses. ‡Includes 1 patient randomized to ipilimumab plus gp100 who received only gp100.