Supplementary Appendix

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

Supplement to: Eggermont AMM, Chiarion-Sileni V, Grob J-J, et al. Prolonged survival in stage III melanoma with ipilimumab adjuvant therapy. N Engl J Med 2016;375:1845-55. DOI: 10.1056/NEJMoa1611299

Supplementary Appendix

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Supplementary statistical considerations

Time-to-event distributions were estimated using the Kaplan-Meier method. The medians of these distributions were presented with their 95% confidence interval (CI) based on the Brookmeyer and Crowley method. Comparisons between treatment groups were done using a log-rank test stratified by stage at randomization, at 2-sided alpha levels as indicated in the body text. Using a Cox proportional hazards model stratified by stage, the hazard ratio for having a recurrence-free survival, overall survival, or distant metastasis-free survival event in the ipilimumab group as compared to the placebo group, and corresponding CIs at the 95.0%, 95.1% or 95.8% levels, were computed. There was no evidence of significant departure from the assumption of proportional hazards for the main comparisons reported in the manuscript.

The main analyses of the efficacy end points were performed on all patients randomized, using the intention-to-treat principle. The safety profile was assessed in patients who started treatment allocated by randomization, and only descriptive statistics were done.

Sensitivity analyses were performed on per-protocol-treatment population (PPT, eligible patients who started the treatment allocated at randomization), or treatment comparison was stratified by staging as reported on the case report forms instead of the one provided at randomization, or treatment comparison was adjusted by variables as reported on the case report forms (see below the list of variables considered; in addition, Breslow thickness ($\leq$2, >2-4 or Unknown, >4 mm)). For the latter analysis, the usual Cox model was used.

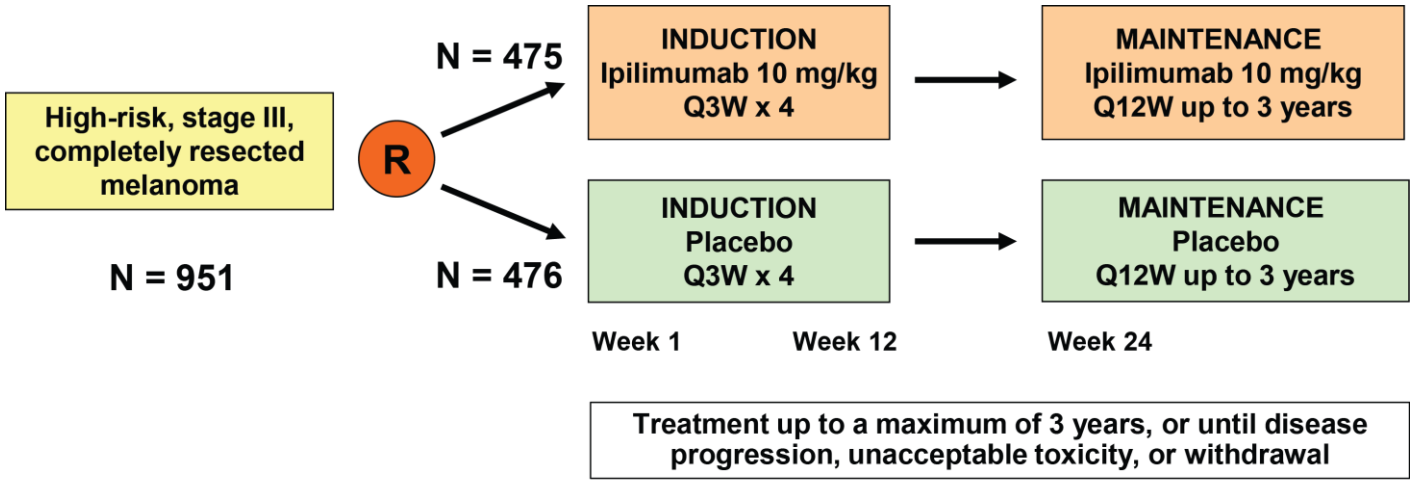
For exploratory purposes, we investigated predictive importance of several factors on the treatment differences regarding the efficacy outcomes. Forest plots technique was used to display treatment differences regarding the time-to-event outcomes (i.e. relapse-free survival and overall survival) within subgroups of given variables. For each subgroup, the treatment hazard ratio and its confidence interval were estimated via the observed (O) and expected (E) number of events, the variance of O-E, which were derived from log-rank test computations.[1]

Heterogeneities between these hazard ratios were tested for significance using the Cochran's Q test, with df degrees of freedom, widely used in meta-analyses.[1] The I^2 (= 100% x (Q – df)/Q)) provided a measure of heterogeneity.[2] An I^2 between 50% and 70% suggests a moderate heterogeneity between the treatment differences observed within 2 or more categories of a variable which was analyzed. Generally, the results of the Cochran's Q test are very close to the one provided by the test of interaction in the Cox model. Both tests have relatively low power in the setting of a clinical trial, indicating that, when their results are only borderline significant, it represents, however, a signal of heterogeneity (interaction) between the treatment outcome differences according to the levels of a given variable.

For the subgroup analyses, the following variables were considered, as they were initially described in the protocol as possible prognostic factors: AJCC staging (Stage IIIA, Stage IIIB, Stage IIIC (1-3 positive lymph nodes), Stage IIIC (4 or more positive lymph nodes)), number of lymph nodes (1, 2-3, 4 or more), type of lymph node involvement (microscopic involvement, i.e. sentinel node positive only, vs macroscopic involvement, i.e. palpable nodes), ulceration status of primary tumor (no ulceration, ulceration, unknown); in addition type of lymph node involvement and ulceration status of primary tumor (microscopic and ulcerated, macroscopic and ulcerated, microscopic and non-ulcerated, macroscopic and non-ulcerated) was considered, in order to investigate whether similar findings are obtained as in the EORTC 18952 and 18991 studies,[3] and to repeat the subgroup analysis performed previously, in this study, for the relapse-free survival endpoint, only.[4] For subgroup analysis, the estimated treatment hazard ratio was plotted along with its 99% CI. No adjustments for multiple end points were done.

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC), and the new sample size computations were done using EAST 6.2.

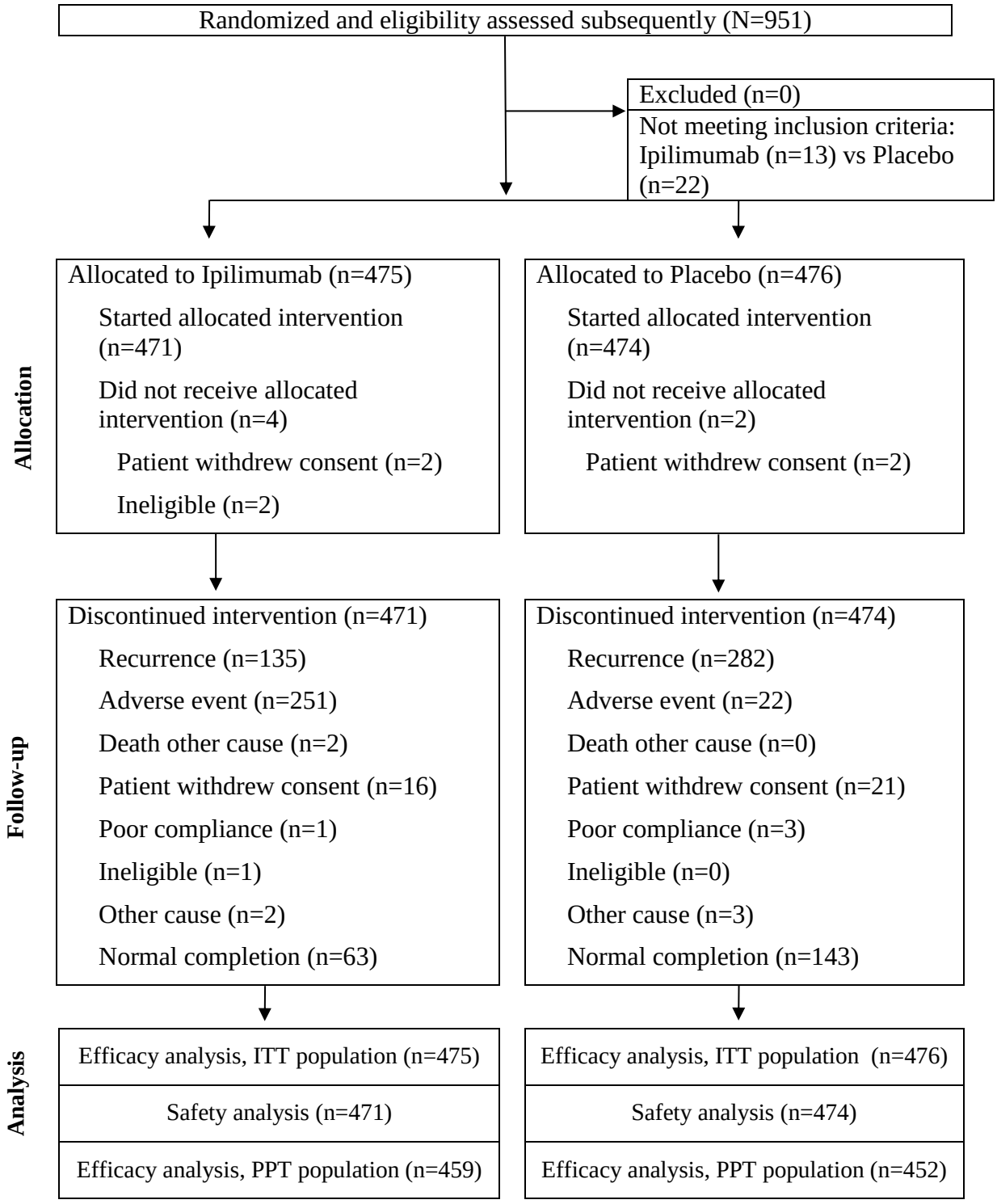
Figure S1. EORTC 18071: Study design.



Stratification factors:

- Stage (IIIA vs IIIB vs IIIC 1-3 positive lymph nodes vs IIIC ≥4 positive lymph nodes)
- Regions (North America, European countries, and Australia)

Figure S2. CONSORT flow diagram.



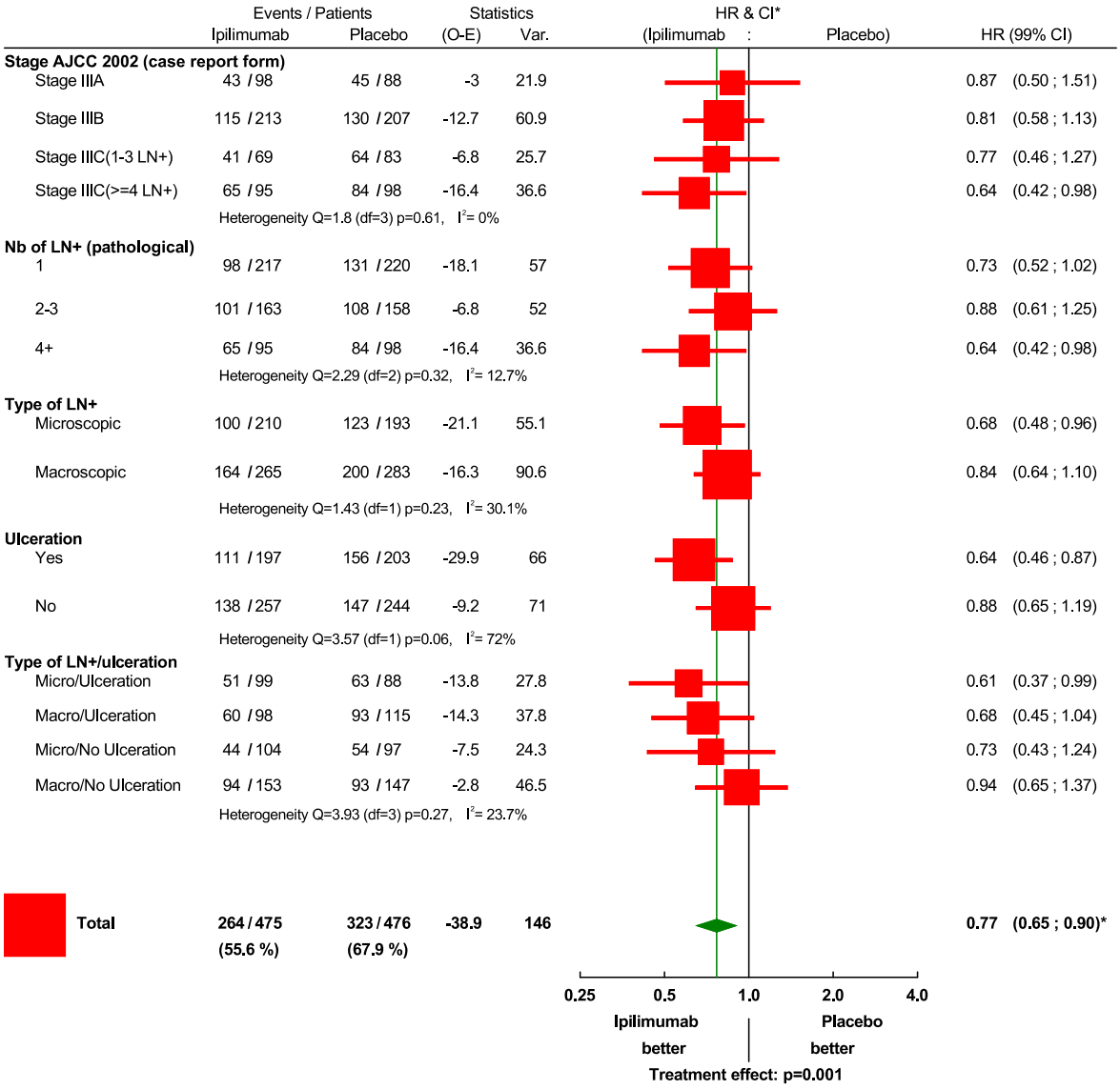
ITT: intent-to-treat population

PPT, per protocol treatment population: eligible patients who started the treatment allocated at randomization

Figure S3. Forest plots for recurrence-free survival (RFS) per independent review committee by treatment group

(A) All patients

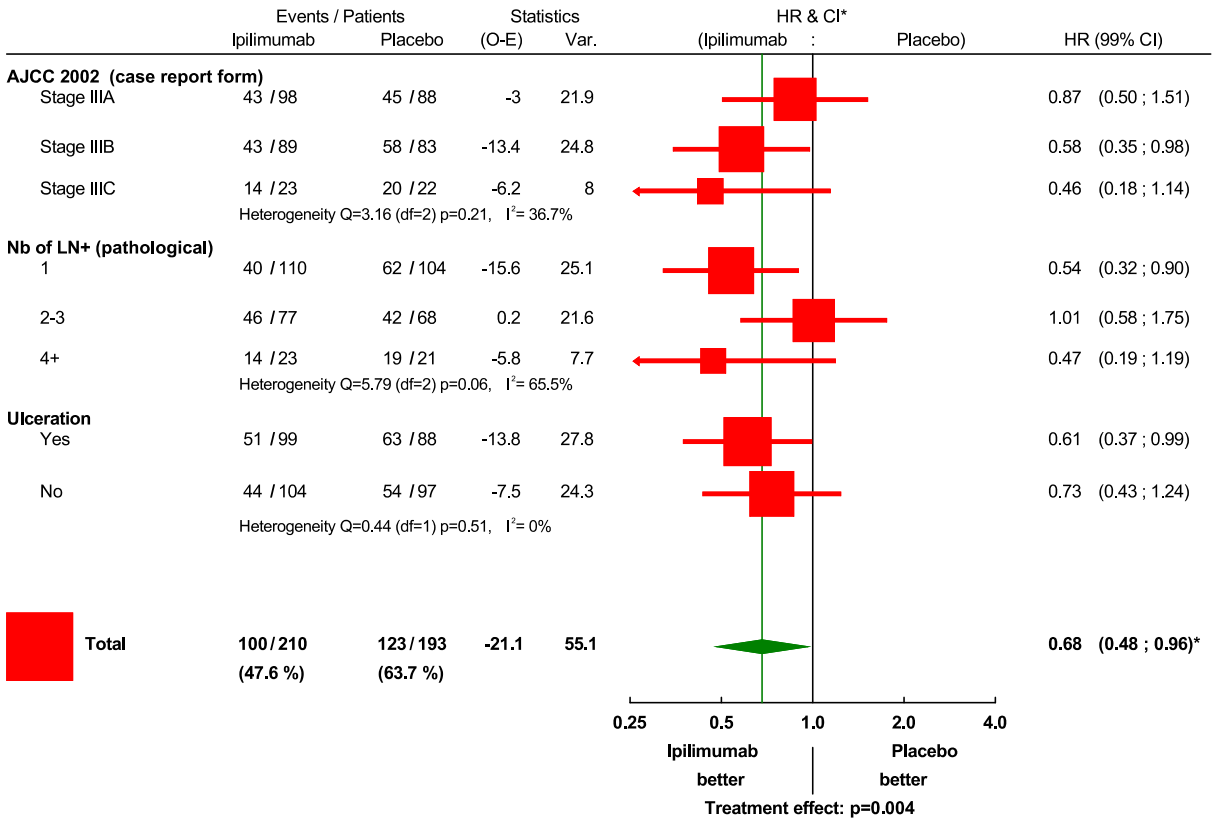
Results are expressed as unstratified hazard ratios for the risk of recurrence or death in the ipilimumab group compared with the placebo group, with 95% or 99% confidence intervals.



*95% CI for totals and subtotals, 99% CI elsewhere

(B) Patients with a microscopic lymph node involvement

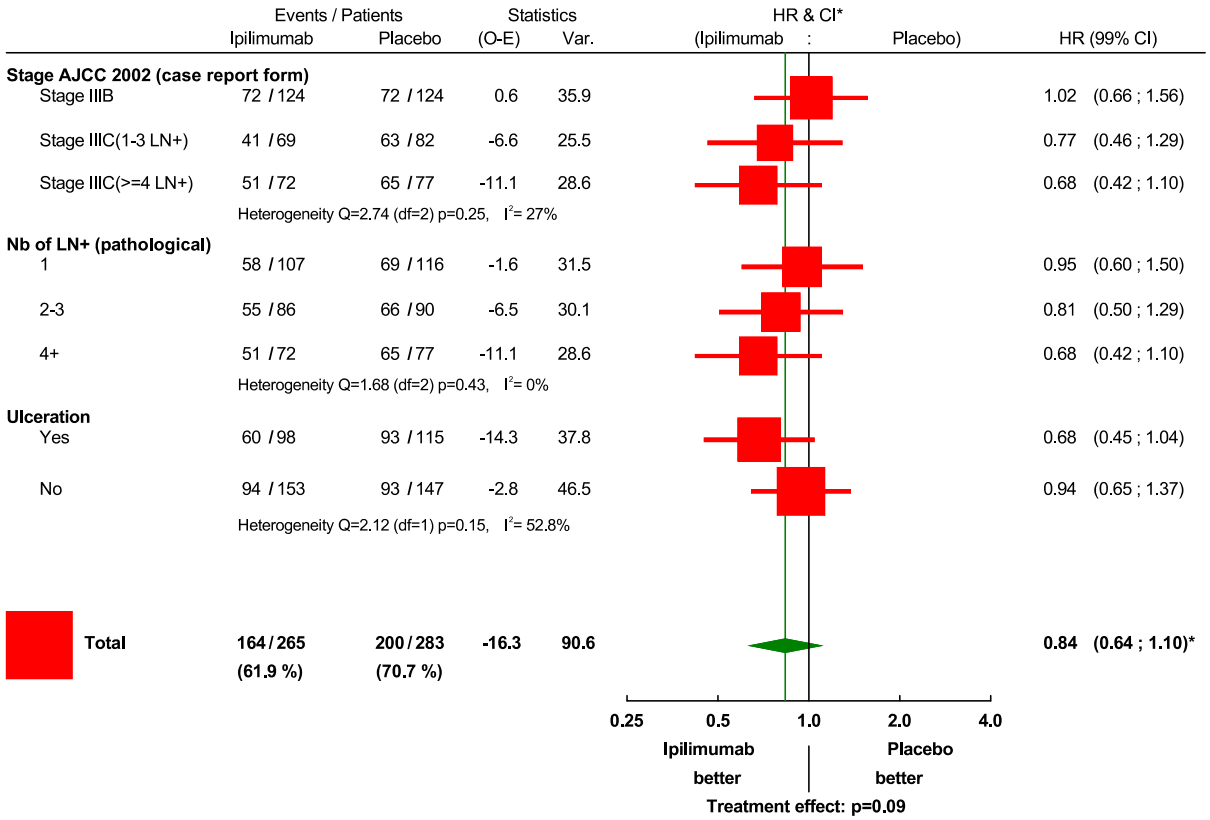
Results are expressed as unstratified hazard ratios for the risk of recurrence or death in the ipilimumab group compared with the placebo group, with 99% confidence intervals.



*99% CI for totals and subtotals, 99% CI elsewhere

(C) Patients with a macroscopic lymph node involvement

Results are expressed as unstratified hazard ratios for the risk of recurrence or death in the ipilimumab group compared with the placebo group, with 99% confidence intervals.

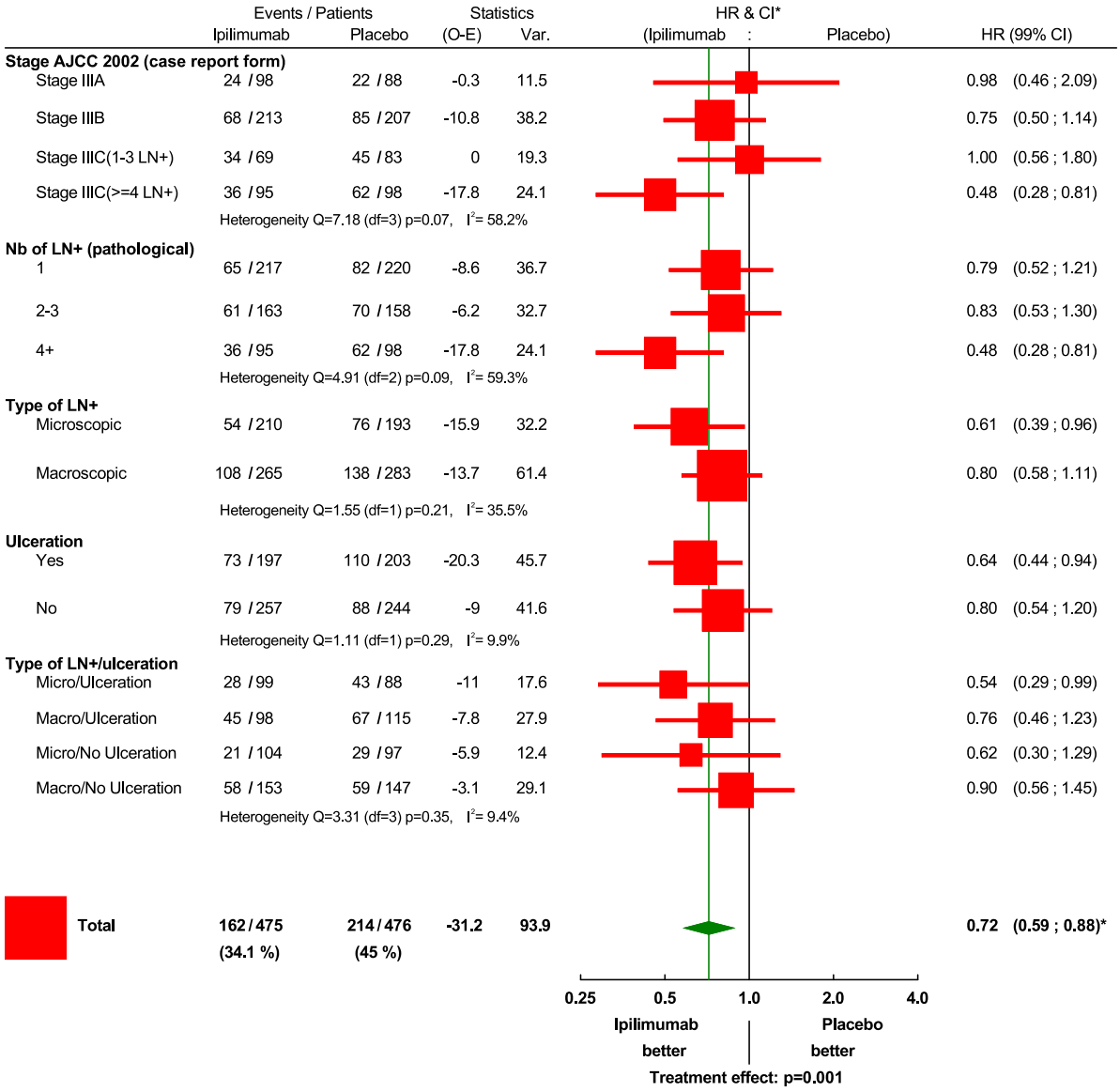


*99% CI for totals and subtotals, 99% CI elsewhere

Figure S4. Forest plots for overall survival

(A) All patients

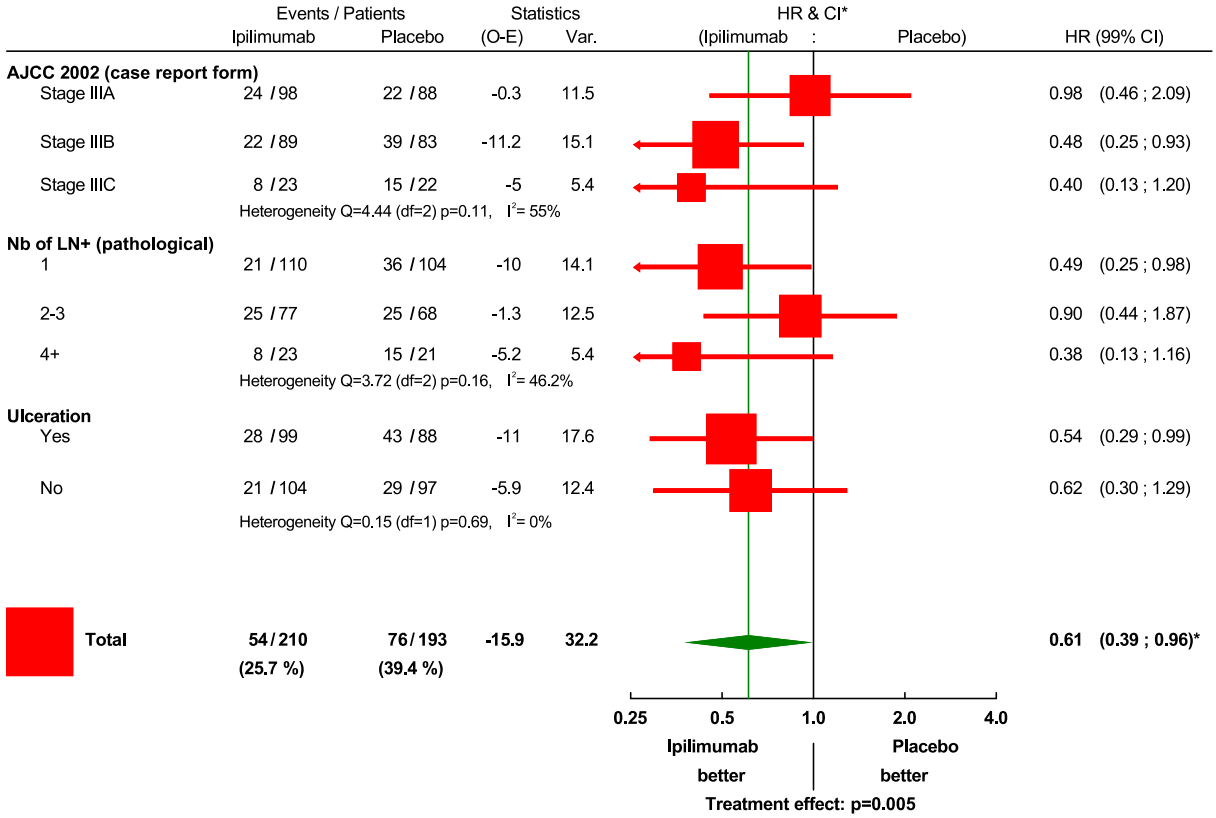
Results are expressed as unstratified hazard ratios for the risk of death in the ipilimumab group compared with the placebo group, with 95% or 99% confidence intervals.



*95% CI for totals and subtotals, 99% CI elsewhere

(B) Patients with a microscopic lymph node involvement.

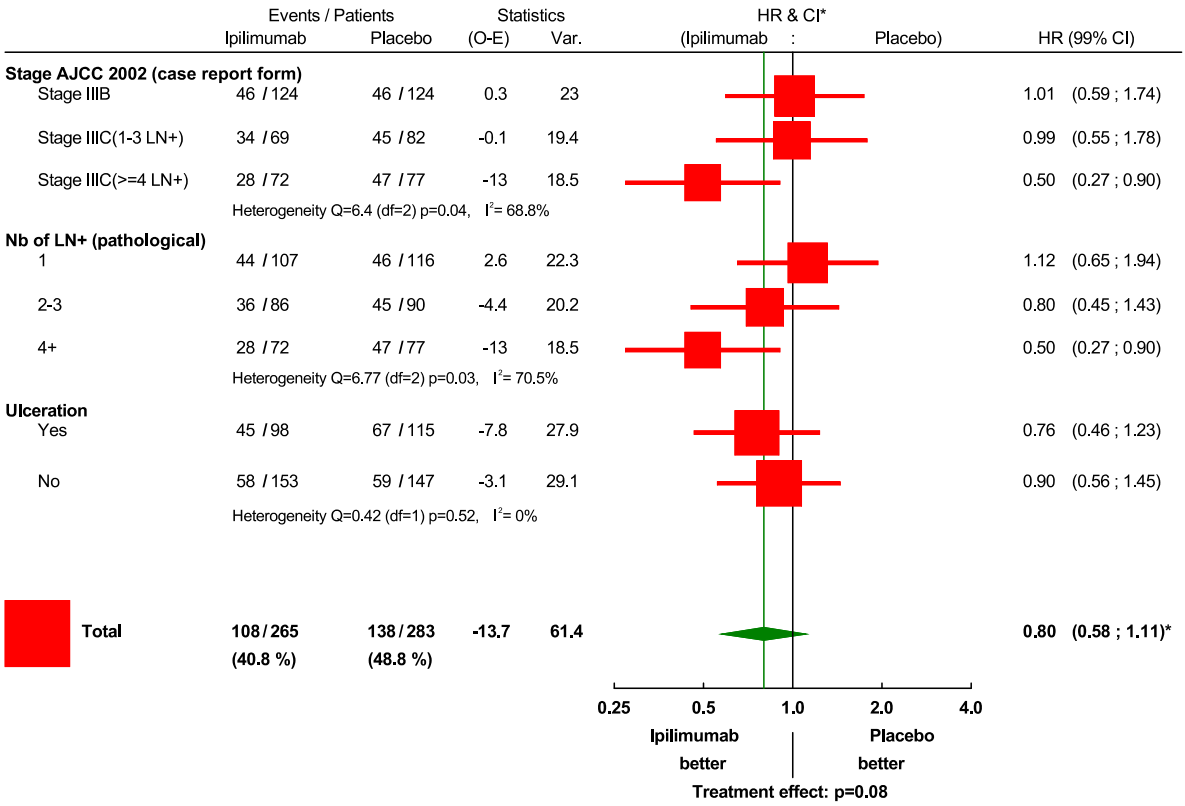
Results are expressed as unstratified hazard ratios for the risk of death in the ipilimumab group compared with the placebo group with 99% confidence intervals.



*99% CI for totals and subtotals, 99% CI elsewhere

(C) Patients with a macroscopic lymph node involvement

Results are expressed as unstratified hazard ratios for the risk of death in the ipilimumab group compared with the placebo group with 99% confidence intervals.



*99% CI for totals and subtotals, 99% CI elsewhere

Table S1. Adverse events.*

	Ipilimumab (N = 471)				Placebo (N = 474)			
Adverse event, %	All grades	Grade 3	Grade 4	Grade 5†	All grades	Grade 3	Grade 4	Grade 5†
All adverse events, regardless of cause								
Any event	465 (98.7)	215 (45.6)	40 (8.5)	7 (1.5)	432 (91.1)	109 (23.0)	15 (3.2)	6 (1.3)
Gastrointestinal disorders								
Diarrhea	232 (49.3)	47 (10.0)	0	0	143 (30.2)	10 (2.1)	0	0
Nausea	117 (24.8)	1 (0.2)	0	0	83 (17.5)	0	0	0
Abdominal pain	66 (14.0)	2 (0.4)	0	0	45 (9.5)	1 (0.2)	0	0
Vomiting	62 (13.2)	2 (0.4)	0	0	28 (5.9)	1 (0.2)	0	0
Colitis	72 (15.3)	31 (6.6)	4 (0.8)	3 (0.6)	6 (1.3)	1 (0.2)	0	0
Dermatologic								
Pruritus	204 (43.3)	11 (2.3)	0	0	70 (14.8)	0	0	0
Rash	186 (39.5)	6 (1.3)	0	0	80 (16.9)	0	0	0
Hepatic								
Alanine aminotransferase increased	102 (21.7)	19 (4.0)	6 (1.3)	0	26 (5.5)	0	0	0
Aspartate aminotransferase increased	78 (16.6)	18 (3.8)	2 (0.4)	0	26 (5.5)	0	0	0
Endocrine disorders								
Hypophysitis	78 (16.6)	20 (4.2)	1 (0.2)	0	2 (0.4)	0	0	0
Hypothyroidism	48 (10.2)	1 (0.2)	0	0	7 (1.5)	0	0	0

Other								
Fatigue	189 (40.1)	9 (1.9)	1 (0.2)	0	143 (30.2)	6 (1.3)	1 (0.2)	0
Headache	152 (32.3)	4 (0.8)	0	0	86 (18.1)	1 (0.2)	0	0
Weight loss	149 (31.6)	1 (0.2)	0	0	42 (8.9)	2 (0.4)	0	0
Pyrexia	82 (17.4)	5 (1.1)	0	0	23 (4.9)	1 (0.2)	0	0
Weight increased	71 (15.1)	2 (0.4)	0	0	114 (24.1)	2 (0.4)	0	0
Cough	68 (14.4)	0	0	0	48 (10.1)	0	0	0
Decreased appetite	65 (13.8)	1 (0.2)	0	0	16 (3.4)	1 (0.2)	0	0

*The safety analysis included all patients who underwent randomization and received at least one dose of study drug (945 patients). Adverse events that occurred in at least 10% of patients are reported. Patients may have had more than one event. †In the ipilimumab group, two patients died because of a non-drug related adverse event (sudden death and malignant melanoma) and five died because of drug-related adverse events; three patients died because of colitis (two with gastrointestinal perforation), one because of myocarditis, and one because of multiorgan failure with Guillain-Barre syndrome; in the placebo group, five patients died because of melanoma-related cause and one had no clear diagnosis.

Table S2. Grade 2-5 irAEs: incidence, time to onset, number resolved, time to resolution.*

	Ipilimumab (N=471)	**Placebo (N=474)**
Skin irAE		
Events – no. (%)	127 (27.0)	15 (3.2)
Median (range) time to onset, wks	4.0 (0.3-155.4)	10.4 (0.3-133.7)
Resolved – no. (%)	117 (92.1)	14 (93.3)
Median (95% CI) time to resolution*, wks	4.9 (3.9-8.1)	2.7 (0.7-6.0)
Gastrointestinal irAE		
Events – no. (%)	145 (30.8)	18 (3.8)
Median (range) time to onset, wks	6.3 (0.3-145.3)	10.3 (0.1-111.6)
Resolved – no. (%)	137 (94.5)	17 (94.4)
Median (95% CI) time to resolution*, wks	4.0 (2.7-5.1)	0.9 (0.4-1.9)
Hepatic irAE		
Events – no. (%)	78 (16.6)	4 (0.8)
Median (range) time to onset, wks	8.9 (1.9-145.4)	22.1 (8.9-110.1)
Resolved – no. (%)	76 (97.4)	4 (100.0)
Median (95% CI) time to resolution*, wks	4.4 (3.4-7.7)	7.1 (1.1-22.1)
Endocrine irAE		
Events – no. (%)	136 (28.9)	7 (1.5)
Median (range) time to onset, wks	10.2 (0.3-165.4)	33.1 (11.9-106.3)
Resolved – no. (%)	70 (51.5)	4 (57.1)
Median (95% CI) time to resolution*, wks	54.3 (18.4-NR)	25.0 (3.4-NR)
Neurological irAE		
Events – no. (%)	11 (2.3)	1 (0.2)
Median (range) time to onset, wks	13.1 (5.9-121.0)	56.3
Resolved – no. (%)	9 (81.8)	0
Median (95% CI) time to resolution*, wks	8.0 (1.1-31.1)	NR

*Time to resolution was from the onset date of an AE. Median and 95% CIs were calculated with the Kaplan-Meier method.

NR: not reached

References

1. Early Breast Cancer Trialists' Collaborative Group. *Treatment of Early Breast Cancer. Vol 1: Worldwide Evidence 1985-1990.* Oxford, UK: Oxford University Press; 1990.

2. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *Br Med J* 2003;327:557-60.

3. Eggermont AMM, Suciu S, Testori A, et al. Ulceration and stage are predictive of interferon efficacy in melanoma: Results of the phase III adjuvant trials EORTC 18952 and EORTC 18991. *Eur J Cancer* 2012;48:218-25.

4. Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. *Lancet Oncol* 2015;16:522-30.