Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial

Alexander M M Eggermont, Vanna Chiarion-Sileni, Jean-Jacques Grob, Reinhard Dummer, Jedd D Wolchok, Henrik Schmidt, Omid Hamid, Caroline Robert, Paolo A Ascierto, Jon M Richards, Céleste Lebbé, Virginia Ferraresi, Michael Smylie, Jeffrey S Weber, Michele Maio, Cyril Konto, Axel Hoos, Veerle de Pril, Ravichandra Karra Gurunath, Gaetan de Schaetzen, Stefan Suciu, Alessandro Testori

Summary

Background Ipilimumab is an approved treatment for patients with advanced melanoma. We aimed to assess ipilimumab as adjuvant therapy for patients with completely resected stage III melanoma at high risk of recurrence.

Methods We did a double-blind, phase 3 trial in patients with stage III cutaneous melanoma (excluding lymph node metastasis ≤1 mm or in-transit metastasis) with adequate resection of lymph nodes (ie, the primary cutaneous melanoma must have been completely excised with adequate surgical margins) who had not received previous systemic therapy for melanoma from 91 hospitals located in 19 countries. Patients were randomly assigned (1:1), centrally by an interactive voice response system, to receive intravenous infusions of 10 mg/kg ipilimumab or placebo every 3 weeks for four doses, then every 3 months for up to 3 years. Using a minimisation technique, randomisation was stratified by disease stage and geographical region. The primary endpoint was recurrence-free survival, assessed by an independent review committee, and analysed by intention to treat. Enrollment is complete but the study is ongoing for follow-up for analysis of secondary endpoints. This trial is registered with EudraCT, number 2007-001974-10, and ClinicalTrials.gov, number NCT00636168.

Findings Between July 10, 2008, and Aug 1, 2011, 951 patients were randomly assigned to ipilimumab (n=475) or placebo (n=476), all of whom were included in the intention-to-treat analyses. At a median follow-up of 2·74 years (IQR 2·28–3·22), there were 528 recurrence-free survival events (234 in the ipilimumab group *vs* 294 in the placebo group). Median recurrence-free survival was 26·1 months (95% CI 19·3–39·3) in the ipilimumab group versus 17·1 months (95% CI 13·4–21·6) in the placebo group (hazard ratio 0·75; 95% CI 0·64–0·90; p=0·0013); 3-year recurrence-free survival was 46·5% (95% CI 41·5–51·3) in the ipilimumab group versus 34·8% (30·1–39·5) in the placebo group. The most common grade 3–4 immune-related adverse events in the ipilimumab group were gastrointestinal (75 [16%] *vs* four [<1%] in the placebo group), hepatic (50 [11%] *vs* one [<1%]), and endocrine (40 [8%] *vs* none). Adverse events led to discontinuation of treatment in 245 (52%) of 471 patients who started ipilimumab (182 [39%] during the initial treatment period of four doses). Five patients (1%) died due to drug-related adverse events. Five (1%) participants died because of drug-related adverse events in the ipilimumab group; three patients died because of colitis (two with gastrointestinal perforation), one patient because of myocarditis, and one patient because of multiorgan failure with Guillain-Barré syndrome.

Interpretation Adjuvant ipilimumab significantly improved recurrence-free survival for patients with completely resected high-risk stage III melanoma. The adverse event profile was consistent with that observed in advanced melanoma, but at higher incidences in particular for endocrinopathies. The risk–benefit ratio of adjuvant ipilimumab at this dose and schedule requires additional assessment based on distant metastasis-free survival and overall survival endpoints to define its definitive value.

Funding Bristol-Myers Squibb.

Introduction

The rapidly rising incidence of cutaneous melanoma has also led to an increased number of patients with regional positive lymph nodes (stage III disease) being diagnosed each year.[1] Breslow thickness, mitotic index, and ulceration of primary melanoma are the strongest prognostic factors for the presence of micrometastasis in regional lymph nodes.[2] The likelihood of systemic metastatic disease in patients with regional lymph node metastasis is closely associated with microscopic versus palpable nodal disease and with number of positive nodes.[3] In an analysis of 3307 patients by the American Joint Committee on Cancer (AJCC),[2] 5-year melanoma-specific survival was 78% for stage IIIA, 59% for stage IIIB, and 40% for stage IIIC melanoma. Recurrence at 5 years has been reported to be 37% in patients with stage IIIA disease, 68% for IIIB disease, and 89% for patients with stage IIIC disease.[4] Even within the sentinel node-positive patient population, heterogeneity is remarkable and is closely associated with tumour load in the sentinel node, as defined by the

Lancet Oncol 2015

Published Online
April 1, 2015
http://dx.doi.org/10.1016/S1470-2045(15)70122-1

See Online/Comment
http://dx.doi.org/10.1016/S1470-2045(15)70162-2

Gustave Roussy Cancer Campus Grand Paris, Villejuif, France (Prof A M M Eggermont MD, Prof C Robert MD); **IOV-IRCCS, Melanoma Oncology Unit, Padova, Italy** (V Chiarion-Sileni MD); **Aix-Marseille University, Hôpital de La Timone APHM, Marseille, France** (Prof J-J Grob MD); **University of Zürich Hospital, Zürich, Switzerland** (Prof R Dummer MD); **Memorial Sloan-Kettering Cancer Center, New York, NY, USA** (J D Wolchok MD); **Aarhus University Hospital, Aarhus, Denmark** (H Schmidt MD); **The Angeles Clinic and Research Institute, Los Angeles, CA, USA** (O Hamid MD); **Istituto Nazionale Tumori Fondazione G Pascale, Naples, Italy** (Prof P A Ascierto MD); **Oncology Specialists SC, Park Ridge, IL, USA** (J M Richards MD); **Assistance Publique Hôpitaux de Paris, Dermatology and CIC Departments, Hôpital Saint Louis, University Paris 7, INSERM U976, France** (Prof C Lebbé MD); **Istituti Fisioterapici Ospitalieri, Rome, Italy** (V Ferraresi MD); **Cross Cancer Institute, Edmonton, Alberta, Canada** (M Smylie MD); **H Lee Moffitt Cancer Center, Tampa, FL, USA** (J S Weber MD); **University Hospital of Siena, Istituto Toscano Tumori, Siena, Italy** (M Maio MD); **Bristol-Myers Squibb, Wallingford, CT, USA** (C Konto MD, A Hoos MD); **Bristol-Myers Squibb,**

Braine-l'Alleud, Belgium (V de Pril MSc); **EORTC Headquarters, Brussels, Belgium** (R K Gurunath MD, G de Schaetzen PhD, S Suciu PhD); **and European Institute of Oncology, Milan, Italy** (A Testori MD)

Correspondence to: Prof Alexander M M Eggermont, Gustave Roussy Cancer Campus Grand Paris and University Paris-Sud, 114 Rue Edouard Vaillant, 94805 Villejuif, France **alexander.eggermont@gustaveroussy.fr**

Research in context

Systematic review

The final protocol for this trial was submitted in January, 2008. In the preceding 2 years we assessed the scientific literature, restricted to English language publications, on PubMed (1980–2007), on adjuvant therapy in melanoma in patients with high risk for recurrence. A simple literature search using the search terms "melanoma", "adjuvant therapy", and "randomised trial" provided all relevant studies.

Added value of the study

This trial is, to the best of our knowledge, the first to assess an approved drug with an effect on survival in advanced melanoma in the adjuvant setting, and the first to study an immune checkpoint inhibitor in this setting. Our findings show that adjuvant use of ipilimumab has a significant effect on recurrence-free survival in the intention-to-treat population. We noted efficacy of the treatment across subgroups including those with palpable lymph nodes. Nevertheless, our results show important side-effects, in particular grade 3–4 colitis and hypophysitis. Our data neither support nor refute the need for maintenance treatment with ipilimumab. However, the effect on recurrence-free survival is potentially better than that of adjuvant interferon.

Interpretation

Ipilimumab is an active drug in the adjuvant setting in patients with high-risk disease, although side-effects are significant. In view of its activity across subgroups including those with high tumour burden, it represents an option in the current adjuvant landscape for those who have experience with administering the drug. Overall survival data are not yet mature and will be reported in the future.

Rotterdam criteria.[5–7] Patients with a metastasis bigger than 1 mm have a highly significant increased risk of recurrence and death than do patients with a metastasis 1 mm or smaller.[5–7]

Ipilimumab, a fully human monoclonal antibody that blocks CTLA-4 to augment anti-tumour immune responses, is an approved treatment for advanced melanoma because of its effect on overall survival.[8–10] The unmet need for an improved adjuvant treatment for melanoma is shown by the hazard ratio (HR) for recurrence or death of 0·83–0·85 with high-dose or low-dose interferon compared with observation only.[11] Interferon is approved in both the USA and the EU as an adjuvant therapy for resected melanoma; however, the treatment is not widely regarded as the standard of care. In the current context of only marginally effective adjuvant therapies with interferons, without a demonstrable dose–response or duration–response effect in meta-analyses,[11–13] the study of ipilimumab in the adjuvant setting is appropriate.

See Online for appendix

Here, we report results from the European Organisation for Research and Treatment of Cancer (EORTC) 18071 trial of adjuvant ipilimumab in high-risk patients with stage III cutaneous melanoma after having undergone a complete regional lymph node dissection.

Methods

Study design and patients

In this multinational, randomised, double-blind, phase 3 trial done in 91 hospitals located in 19 countries, eligible patients were at least 18 years of age and had histologically confirmed melanoma metastatic to lymph nodes only. According to the AJCC 2009 (for stage III identical to AJCC 2002) classification, patients had to have either stage IIIA melanoma (if N1a, at least 1 metastasis >1 mm), stage IIIB or stage IIIC, with no in-transit metastasis.[2] The primary cutaneous melanoma must have been completely excised with adequate surgical margins. Complete regional lymphadenectomy was required within the 12 weeks before randomisation. Exclusion criteria included unknown primary, ocular, or mucosal melanoma, Eastern Cooperative Oncology Group (ECOG) performance status greater than 1, autoimmune disease, uncontrolled infections, cardiovascular disease, white blood cell count lower than $2·5\times10^9$ cells per L, absolute neutrophil count lower than $1·0\times10^9$ cells per L, platelets lower than 75×10^9 cells per L, haemoglobin concentration less than 9 g/dL, creatinine higher than 2·5 times the upper normal limit, hepatic enzymes or lactate dehydrogenase higher than two times the upper normal limit, use of systemic corticosteroids, and previous systemic therapy for melanoma.

The protocol (appendix) was approved by the EORTC protocol review committee and independent ethics committees. The study was done in accordance with the ethical principles originating from the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonization. All participating patients gave written informed consent.

Randomisation and masking

Patients were randomly assigned (1:1) to receive either ipilimumab or placebo (appendix). Registration was done centrally at the EORTC headquarters. We used a central interactive voice response system (Worldwide Clinical Trials, Beverly Hills, CA, USA) for drug accountability and central randomisation, based on a minimisation technique.[14] Patients were stratified by disease stage (stage IIIA *vs* stage IIIB *vs* stage IIIC with one to three positive nodes *vs* stage IIIC with four or more positive nodes) and regions (North America, European countries, and Australia). The local pharmacist did the randomisation and was unmasked for allocated treatment.

Clinical investigators and those collecting or analysing the data were masked to treatment group assignment.

Procedures

Patients received either intravenous infusions of 10 mg/kg or placebo every 3 weeks for four doses, then every 3 months for up to a maximum of 3 years, or until disease recurrence, unacceptable toxicity, major protocol violation, or treatment refusal. After the initial four doses (induction) of ipilimumab or placebo, additional therapy (maintenance) was added based on the theoretical principles of continued re-stimulation of the immune system, consistent with previous studies of immunotherapy in adjuvant melanoma.[12] Rules regarding the withholding of a dose of ipilimumab or placebo and management of immune-related adverse events are detailed in the protocol (appendix).

Patients in both study groups were planned to be assessed for recurrence and distant metastases every 3 months during the first 3 years and every 6 months thereafter. Physical examination, chest radiography, CT, or other imaging techniques were used as clinically indicated. Patients were assessed at baseline during the screening phase, within maximum 6 weeks before randomisation. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed irrespective of the method of assessment. An independent review committee, whose members were kept masked of study-group assignments, assessed disease status and date of recurrence.

Outcomes

The primary endpoint was recurrence-free survival, as assessed by the independent review committee. Secondary endpoints were distant-metastasis free survival (also assessed by the independent review committee; appendix), overall survival, adverse event profile, and health-related quality of life (assessed with EORTC QLQ-C30 instrument). Recurrence-free survival was defined as the time between the date of randomisation and the date of first recurrence (local, regional, or distant metastasis) or death (whatever the cause), whichever occurred first. For patients still alive and without disease recurrence, recurrence-free survival was censored on the date of last disease assessment.

We recorded adverse events for each treatment course with the National Cancer Institute's Common Terminology Criteria for Adverse Events (version 3.0). Based on the report by the local investigator of each adverse event, MedDRA recoding was done during the course of the study. Immune-related adverse events were programmatically established from a predefined list of MedDRA terms, which was updated according to each version of MedDRA. Safety analyses were done in all patients who were randomly assigned to treatment and received at least one dose of study drug (safety population).

Resolution of a grade 3 or 4 immune-related adverse event was defined as an improvement to grade 1 or less, or to the worst grade at baseline. Some patients with grade 1 adverse events were permitted to receive maintenance therapy (criteria shown in protocol). The grade 3 or 4 immune-related adverse event with the longest time to resolution was selected for inclusion in the analysis. If the grade 3 or 4 immune-related adverse event did not resolve, the patient's follow-up was censored at the last known alive date. Similar analyses were repeated for grade 2–5 immune-related adverse events.

Statistical analysis

512 recurrence-free survival events were required to provide 90% power to detect an ipilimumab versus placebo HR of 0·75 (two-sided α of 0·05), corresponding to an increase from 58·3% to 66·% in 1-year recurrence-free survival and from 35·4% to 45·9% in 3-year recurrence-free survival. Therefore, 950 patients were planned to be randomly assigned.

	Ipilimumab group (n=475)	Placebo group (n=476)
Sex		
Male	296 (62%)	293 (62%)
Female	179 (38%)	183 (38%)
Age (years)	51 (20–84)	52 (18–78)
<50 years	214 (45%)	211 (44%)
51–<65 years	180 (38%)	178 (37%)
≥65 years	81 (17%)	87 (18%)
Stage*		
Stage IIIA	98 (21%)	98 (21%)
Stage IIIB	182 (38%)	182 (38%)
Stage IIIC (1–3 LN+)	122 (26%)	121 (25%)
Stage IIIC (≥4 LN+)	73 (15%)	75 (16%)
AJCC 2002†		
Stage IIIA	98 (21%)	88 (18%)
Stage IIIB	213 (45%)	207 (43%)
Stage IIIC (1–3 LN+)	69 (15%)	83 (17%)
Stage IIIC (≥4 LN+)	95 (20%)	98 (21%)
Lymph node involvement†		
Microscopic	210 (44%)	193 (41%)
Macroscopic	265 (56%)	283 (59%)
Number of LN+ (pathological)†		
1	217 (46%)	220 (46%)
2–3	163 (34%)	158 (33%)
≥4	95 (20%)	98 (21%)
Ulceration†		
No	257 (54%)	244 (51%)
Yes	197 (41%)	203 (43%)
Unknown	21 (4%)	29 (6%)

Data are n (%) or n (range). LN+=positive lymph nodes. AJCC=American Joint Committee on Cancer. *As provided at randomisation. †As indicated on case report forms. The appendix shows distribution by region and country.

Table 1: **Demographic and baseline clinical characteristics of the patients**

The Kaplan-Meier technique was used to obtain estimates of the recurrence-free survival distributions, and the 95% CI of these estimates (–1·96×standard error [SE], 1·96×SE), where the SE was computed with the Greenwood formula. Medians were presented with a 95% CI based on the Brookmeyer and Crowley method. We compared the recurrence-free survival distributions of the treatment groups with a log-rank test at a two-sided alpha level of 0·05, stratified by stage as indicated at randomisation. The treatment HR for recurrence or death, and its 95% CI, was estimated with a Cox proportional hazards model, stratified by stage as indicated at randomisation.

The main analysis of the efficacy endpoint was by intention to treat: all patients were deemed at risk of having a recurrence-free survival event until the respective event was reached; follow-up was not censored on purpose for patients who went off-protocol treatment because of, for example, protocol violation, toxicity, and treatment refusal. Forest plot analyses and further exploratory post-hoc subgroup analyses were used to investigate predictive importance of different factors on the treatment difference (appendix). Safety profiles were assessed in patients who started treatment allocated by randomisation, and no statistical inferences were done.

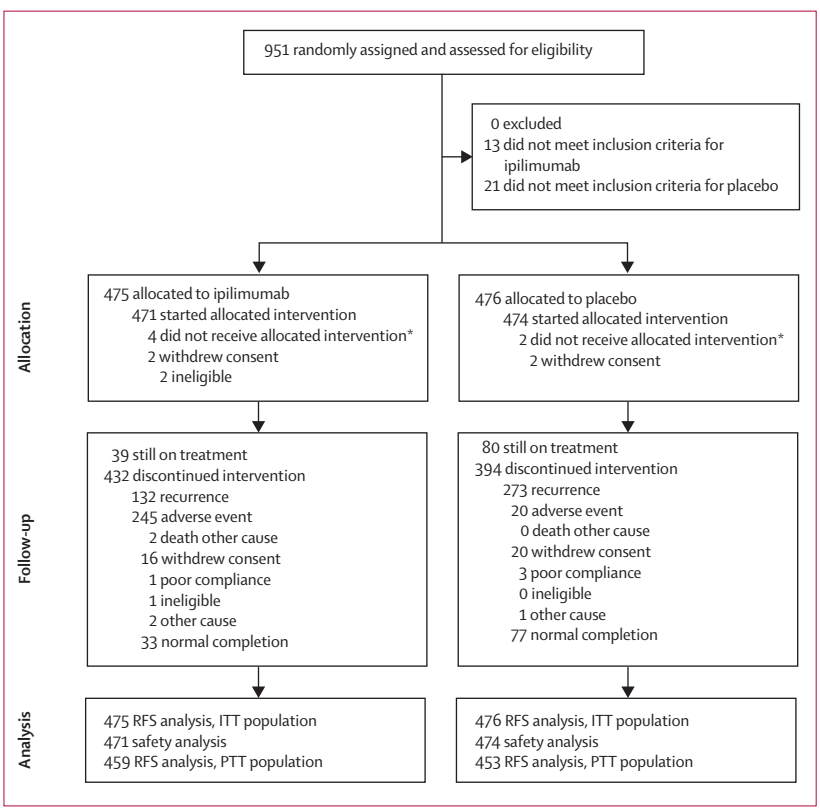

Figure 1: **Trial profile**
RFS=recurrence-free survival. ITT=intention-to-treat. PPT=per-protocol treatment (eligible patients who started the treatment allocated at randomisation). *One patient had follow-up for a long period of time and the other five were lost to follow-up. Because of a lack of disease assessment after randomisation, recurrence-free survival duration was censored at 1 day.

An independent data and safety monitoring board was responsible for safeguarding the interests of patients, assessing the safety data and monitoring the overall conduct of the clinical study. Efficacy was also reviewed by the data and safety monitoring board, as part of the benefit-to-risk assessment, but no formal interim analyses were performed before this final recurrence-free survival analysis. The board met twice a year after the first 100 patients had been randomised and followed up for at least 12 weeks. On-site source data verification was performed via a contract research organisation.

The clinical cutoff date for this analysis was July 26, 2013, and the database was locked in December, 2013. As per the recommendation of the data and safety monitoring board, the study is ongoing for the assessment of distant metastasis-free survival and overall survival; both the investigators and the sponsor remain masked to these data. All analyses were done with SAS software (version 9.2 and 9.3, SAS Institute, Cary, NC, USA). This trial is registered with EudraCT, number 2007-001974-10, and ClinicalTrials.gov, number NCT00636168.

Role of the funding source

The funder and the sponsor of the trial was Bristol-Myers Squibb. The trial was designed jointly by the members of the writing committee (study coordinator, EORTC Headquarters team and Bristol-Myers Squibb representative). Data were collected and computerised at the EORTC Headquarters, and were copied to Bristol-Myers Squibb after database lock. Data were analysed independently at both the EORTC Headquarters (SS) and by Bristol-Myers Squibb (VdP). An initial draft of the manuscript was prepared by the study coordinator and the EORTC trial statistician. All the authors participated in the revision and finalisation of the manuscript, and made the decision to submit the manuscript for publication. After the database lock (ie, at time of final analysis), statisticians had full access to all the data; thereafter the first author (AMME) received the final reports.

Results

Between July 10, 2008, and Aug 1, 2011, 951 patients were randomly assigned (475 in the ipilimumab group and 476 in the placebo group). Table 1 shows patient and disease characteristics. Overall, 186 (20%) patients had stage IIIA, 420 (44%) had stage IIIB, and 345 (36%) had stage IIIC disease; 400 (42%) patients had an ulcerated primary, and 548 (58%) had macroscopic lymph node involvement.

Six patients did not start the allocated treatment by randomisation (figure 1). Of the remaining patients, the median number of doses received per patient in the ipilimumab group was four (range 1–16) and eight (range 1–16) in the placebo group. At least one maintenance dose was received by 198 (42%) of 471 patients in the ipilimumab and 332 (70%) of

	All randomly assigned patients		Microscopic stage III* (positive sentinel nodes)		Macroscopic stage III* (palpable nodes)	
	Ipilimumab group (n=475)	Placebo group (n=476)	Ipilimumab group (n=210)	Placebo group (n=193)	Ipilimumab group (n=265)	Placebo group (n=283)
Median RFS (months)	26·1 (19·3–39·3)	17·1 (13·4–21·6)	NR (38·4–NR)	26·9 (19·3–32·9)	15·4 (11·3–22·9)	11·3 (8·1–16·6)
3-year RFS	46·5% (41·5–51·3)	34·8% (30·1–39·5)	57·6% (50·0–64·4)	39·2% (31·4–47·0)	37·8% (31·3–44·2)	31·7% (25·9–37·5)
HR	0·75 (0·64–0·90)†	..	0·65 (0·45–0·96)†	..	0·81 (0·61–1·08)†	..
p value	0·0013†	..	0·004†	..	0·06†	..

Data are Kaplan-Meier estimate (95% CI) or hazard ratio (95% CI for overall population or 99% CI for subgroup analysis). RFS=recurrence-free survival. NR=not reached. HR=hazard ratio. *Post-hoc subgroup analyses. †Cox model stratified by stage at randomisation. The appendix shows additional information regarding treatment outcomes (eg, 1-year and 2-year RFS, unadjusted HR, and HR adjusted by several factors).

Table 2: **Recurrence-free survival per independent review committee, overall and by type of lymph node involvement**

474 patients in the placebo group. 136 (29%) of 471 patients in the ipilimumab group received at least seven doses (about 1 year of treatment) compared with 269 (57%) of 474 in the placebo group.

Of 471 patients who started ipilimumab, 245 (52%) discontinued treatment because of an adverse event, of which 230 (49%) were drug-related; in 182 (39%) patients the adverse event leading to discontinuation happened within 12 weeks of the start of treatment. Of the 474 patients in the placebo group who received at least one dose of assigned treatment, 20 (4%) discontinued treatment because of an adverse event (figure 1). 132 (28%) patients discontinued ipilimumab because of disease recurrence compared with 273 (58%) patients in the placebo group. 33 (7%) patients in the ipilimumab group and 77 (16%) in the placebo group completed the entire 3-year treatment period; 39 (8%) patients in the ipilimumab group and 80 (17%) in the placebo group were still on treatment on July 26, 2013, the date of clinical cutoff, respectively (figure 1). No dose reductions or modifications were made. The overall median follow-up was 2·74 years (IQR 2·28–3·22), 2·60 years (2·10–3·07) in the ipilimumab group and 2·76 years (2·29–3·26) in the placebo group.

528 recurrence-free survival events were reported (234 in the ipilimumab group and 294 in the placebo group). Recurrence-free survival was significantly longer in the ipilimumab group than in the placebo group (HR, stratified by stage, 0·75, 95% CI 0·64–0·90; p=0·0013; table 2 and figure 2). Median recurrence-free survival in the ipilimumab group was 26·1 months (95% CI 19·3–39·3) versus 17·1 months (13·4–21·6) in the placebo group; 3-year recurrence-free survival was 46·5% (95% CI 41·5–51·3) in the ipilimumab group versus 34·8% (30·1–39·5) in the placebo group.

The effect of ipilimumab on recurrence-free survival was consistent across subgroups (figure 3). An effect on recurrence-free survival was noted irrespective of the number of positive lymph nodes (figure 3), and seemed to be higher in patients with an ulcerated melanoma than in patients with a non-ulcerated melanoma, as suggested by univariate analyses (present *vs* absent; test of heterogeneity p=0·20; figure 3) and analyses stratified by stage (table 3), and confirmed by multivariate analyses (appendix). Therefore, in these post-hoc analyses, the effect of ipilimumab was more prominent in the 345 patients with stage IIIC disease (of whom 228 [66%] had ulcerated melanoma) than in the 420 patients with stage IIIB disease (of whom 172 [41%] had ulcerated melanoma), and also than in the 196 patients with stage IIIA (none of whom had ulcerated melanoma; figure 3). In patients with microscopic involvement, the effect of ipilimumab seemed higher than in patients with macroscopic involvement, as indicated in univariate analyses (figure 3) and analyses stratified by stage (table 3).

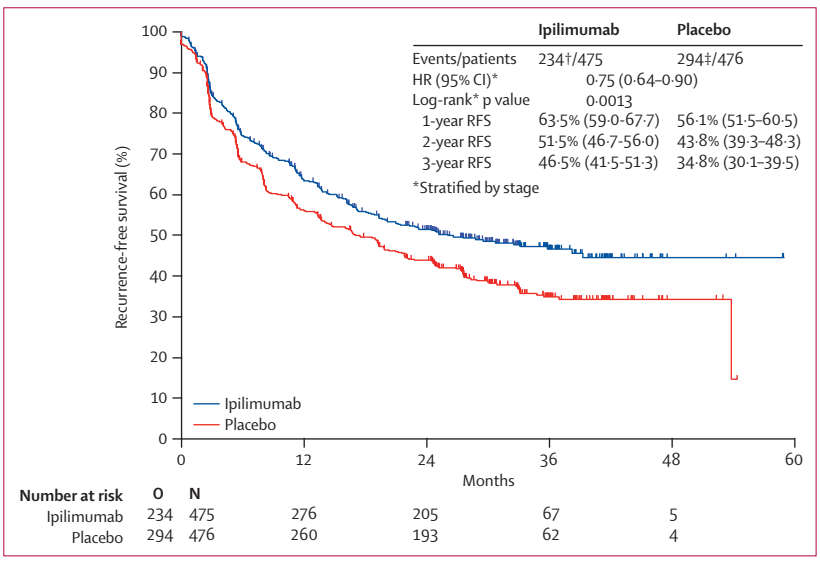

Figure 2: **Kaplan-Meier curves of recurrence-free survival, as assessed by IRC**
RFS=recurrence-free survival. IRC=independent review committee. O=observed number of events (recurrence or death). N=number of patients. *We compared the RFS distributions of the treatment groups with a log-rank test at a two-sided alpha level of 0·05, stratified by stage as indicated at randomisation. †Type of RFS event: locoregional recurrence (n=87), distant metastasis or death due to melanoma (n=138), death due to another cause or unknown cause (n=9). ‡Type of RFS event: locoregional recurrence (n=106), distant metastasis or death due to melanoma (n=186), death due to another cause or unknown cause (n=2).

Sensitivity analyses based on the per-protocol treatment population, or using recurrence-free survival as reported by the investigators, yielded similar results (appendix), as was the case for treatment comparison stratified by stage as given on case report forms (HR 0·76, 95% CI 0·64–0·90; p=0·002). Patients remain in follow-up for the endpoints of distant metastasis-free survival and overall survival.

In the ipilimumab group, 465 (99%) of 471 patients had an adverse event of any grade, with grade 3 or 4 adverse

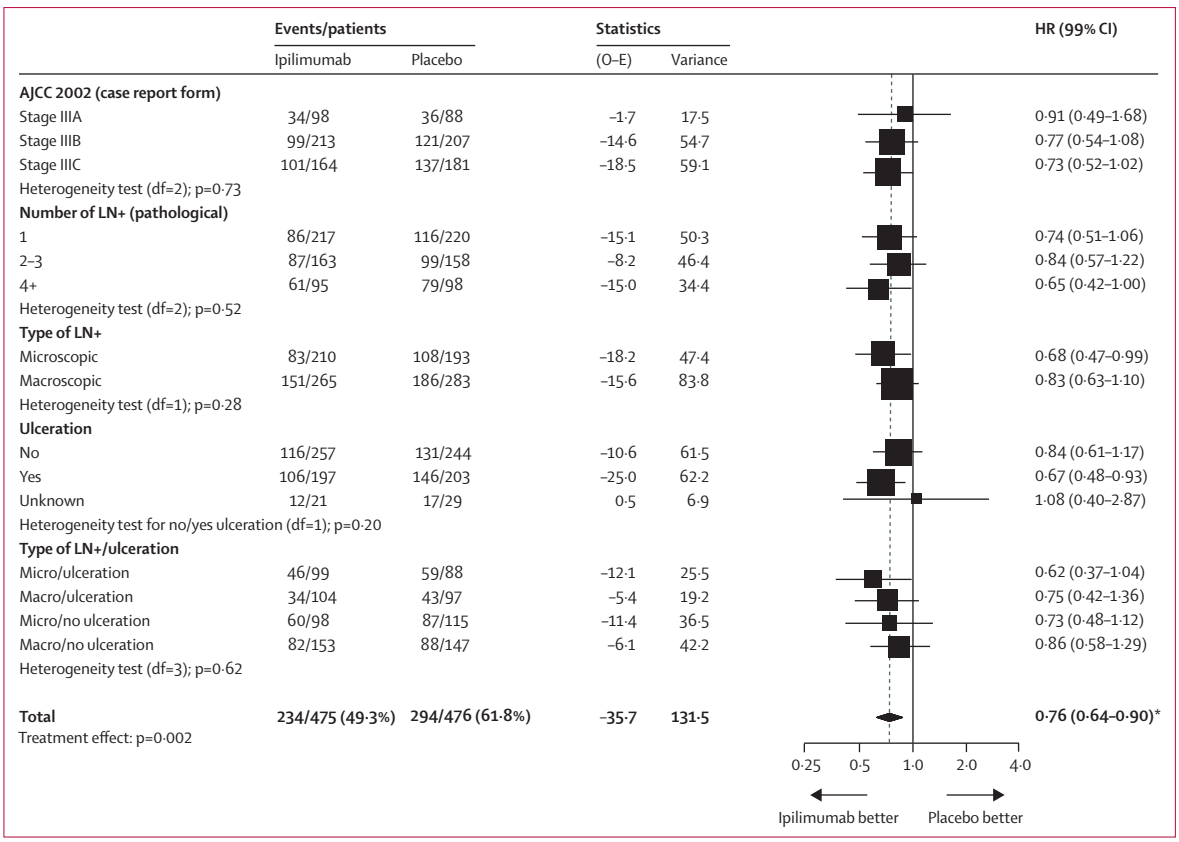

Figure 3: **Subgroup analyses of recurrence-free survival as assessed by IRC**
IRC=independent review committee. O–E=observed–expected number of events (recurrence or death). AJCC=American Joint Committee on Cancer. df=degrees of freedom. LN+=positive lymph nodes. HRs are unstratified. *95% CI for totals, 99% CI elsewhere.

	Microscopic or macroscopic stage III with known ulceration status*		Microscopic stage III* (positive sentinel nodes)		Macroscopic stage III* (palpable nodes)	
	Ulcerated primary (n=400)	Non-ulcerated primary (n=501)	Ulcerated primary (n=187)	Non-ulcerated primary (n=201)	Ulcerated primary (n=213)	Non-ulcerated primary (n=300)
HR (99% CI)*	0·64 (0·46–0·90)	0·84 (0·60–1·17)	0·58 (0·34–0·97)	0·75 (0·41–1·37)	0·70 (0·45–1·08)	0·86 (0·57–1·27)

*Cox model stratified by stage at randomisation.

Table 3: **Post-hoc subgroup analyses of the effect of ipilimumab on recurrence-free survival by type of lymph node involvement and ulceration status of the primary tumour**

events in 254 (54%) patients; 432 (91%) of 474 patients in the placebo group had an adverse event of any grade, with grade 3 or 4 adverse events occurring in 118 (25%) patients (table 4). On-study immune-related adverse events were more frequently reported in the ipilimumab group than in the placebo group (table 4). The most common grade 3–4 immune-related adverse events in the ipilimumab group were gastrointestinal, hepatic, and endocrine in nature (table 4). For all classes, most patients had only one episode of a grade 3–4 immune-related adverse event. The median time to onset of on-study grade 2–5 immune-related adverse events in the ipilimumab group ranged from 4·3 weeks (IQR 1·1–10·6; skin immune-related adverse events) to 13·1 weeks (8·3–77·3; neurological immune-related adverse events; appendix). In the ipilimumab group, excluding endocrine immune-related adverse events, most grade 2–4 immune-related adverse events (82–95%) resolved to baseline or grade 1 with established management algorithms (protocol). The median time to resolution ranged from 4·0 to 8·0 weeks. Endocrine immune-related adverse events resolved in a smaller proportion of ipilimumab-treated patients (75 [56%] of 134 patients) and took longer to resolve (median 31·1 weeks, IQR 8·3–77·3).

Five (1%) participants died because of drug-related adverse events in the ipilimumab group; three patients died because of colitis (two with gastrointestinal perforation), one patient because of myocarditis, and one

	Ipilimumab group (n=471)				Placebo group (n=474)			
	Grade 1–2	Grade 3	Grade 4	Grade 5†	Grade 1–2	Grade 3	Grade 4	Grade 5†
All adverse events, regardless of cause								
Any event	205 (44%)	215 (46%)	39 (8%)	6 (1%)	307 (65%)	103 (22%)	15 (3%)	6 (1%)
Dermatological								
Pruritus	192 (41%)	11 (2%)	0 (0%)	0 (0%)	70 (15%)	0 (0%)	0 (0%)	0 (0%)
Rash	179 (38%)	6 (1%)	0 (0%)	0 (0%)	80 (17%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal disorders								
Diarrhoea	185 (39%)	46 (10%)	0 (0%)	0 (0%)	134 (28%)	9 (2%)	0 (0%)	0 (0%)
Nausea	115 (24%)	1 (<1%)	0 (0%)	0 (0%)	83 (18%)	0 (0%)	0 (0%)	0 (0%)
Colitis	39 (8%)	32 (7%)	4 (<1%)	0 (0%)	5 (1%)	1 (<1%)	0 (0%)	0 (0%)
Abdominal pain	64 (14%)	2 (<1%)	0 (0%)	0 (0%)	44 (9%)	1 (<1%)	0 (0%)	0 (0%)
Vomiting	57 (12%)	2 (<1%)	0 (0%)	0 (0%)	27 (6%)	1 (<1%)	0 (0%)	0 (0%)
Colitis, ulcerative	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Hepatic								
Alanine aminotransferase increased	77 (16%)	19 (4%)	6 (1%)	0 (0%)	26 (5%)	0 (0%)	0 (0%)	0 (0%)
Aspartate aminotransferase increased	58 (12%)	18 (4%)	2 (<1%)	0 (0%)	24 (5%)	0 (0%)	0 (0%)	0 (0%)
Endocrine disorders								
Hypophysitis	63 (13%)	22 (5%)	3 (<1%)	0 (0%)	3 (<1%)	0 (0%)	0 (0%)	0 (0%)
Other								
Fatigue	179 (38%)	9 (2%)	1 (<1%)	0 (0%)	136 (29%)	6 (1%)	1 (<1%)	0 (0%)
Headache	148 (31%)	4 (<1%)	0 (0%)	0 (0%)	85 (18%)	1 (<1%)	0 (0%)	0 (0%)
Weight loss	145 (31%)	2 (<1%)	0 (0%)	0 (0%)	34 (7%)	2 (<1%)	0 (0%)	0 (0%)
Pyrexia	77 (16%)	5 (1%)	0 (0%)	0 (0%)	21 (4%)	1 (<1%)	0 (0%)	0 (0%)
Weight increased	68 (14%)	1 (<1%)	0 (0%)	0 (0%)	109 (23%)	1 (<1%)	0 (0%)	0 (0%)
Cough	68 (14%)	0 (0%)	0 (0%)	0 (0%)	48 (10%)	0 (0%)	0 (0%)	0 (0%)
Decreased appetite	64 (14%)	1 (<1%)	0 (0%)	0 (0%)	15 (3%)	1 (<1%)	0 (0%)	0 (0%)
Immune-related adverse events								
Any immune-related adverse event	226 (48%)	172 (37%)	26 (6%)	2 (<1%)	171 (36%)	11 (2%)	1 (<1%)	0 (0%)
Dermatological	277 (59%)	21 (4%)	0 (0%)	0 (0%)	99 (21%)	0 (0%)	0 (0%)	0 (0%)
Pruritus	176 (37%)	11 (2%)	0 (0%)	0 (0%)	51 (11%)	0 (0%)	0 (0%)	0 (0%)
Rash	156 (33%)	6 (1%)	0 (0%)	0 (0%)	52 (11%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal	142 (30%)	70 (15%)	5 (1%)	1 (<1%)	80 (17%)	3 (<1%)	1 (<1%)	0 (0%)
Diarrhoea	150 (32%)	45 (10%)	0 (0%)	0 (0%)	77 (16%)	2 (<1%)	0 (0%)	0 (0%)
Colitis	39 (8%)	32 (7%)	4 (<1%)	0 (0%)	5 (1%)	1 (<1%)	0 (0%)	0 (0%)
Colitis, ulcerative	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)
Endocrine	137 (29%)	37 (8%)	3 (<1%)	0 (0%)	31 (7%)	0 (0%)	0 (0%)	0 (0%)
Hypophysitis	62 (13%)	22 (5%)	2 (<1%)	0 (0%)	2 (<1%)	0 (0%)	0 (0%)	0 (0%)
Hypothyroidism	41 (9%)	1 (<1%)	0 (0%)	0 (0%)	4 (<1%)	0 (0%)	0 (0%)	0 (0%)
Hepatic	68 (14%)	37 (8%)	13 (3%)	0 (0%)	20 (4%)	1 (<1%)	0 (0%)	0 (0%)
Liver function test increase	68 (14%)	18 (4%)	7 (1%)	0 (0%)	19 (4%)	0 (0%)	0 (0%)	0 (0%)
Neurologic	12 (3%)	5 (1%)	4 (<1%)	0 (0%)	9 (2%)	0 (0%)	0 (0%)	0 (0%)
Other	73 (15.5)	35 (7%)	2 (<1%)	1 (<1%)	13 (3%)	8 (2%)	0 (0%)	0 (0%)
Multiorgan failure	0 (0%)	0 (0%)	0 (0%)	1 (<1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Data are n (%). *The safety analysis included all patients who underwent randomisation and received at least one dose of study drug (945 patients). Adverse events and immune-related adverse events that occurred in at least 10% of patients are reported. Patients might have had more than one event. †In the Ipilimumab group, one patient died because of a non-drug related adverse event (sudden death) 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-Barré syndrome; in the placebo group, five patients died because of melanoma-related cause and one had no clear diagnosis..

Table 4: **Adverse events in the safety population***

patient because of multiorgan failure with Guillain-Barré syndrome. These deaths occurred before the start of maintenance therapy. Four patients received corticosteroids and one anti-TNF antibodies. No deaths were deemed to be treatment related in the placebo group. Quality of life data will be presented in another report.

Discussion

Our data show that 10 mg/kg ipilimumab for up to 3 years as adjuvant treatment in patients with adequate resection of lymph nodes and high-risk stage III melanoma significantly improved recurrence-free survival, the primary endpoint of the trial, compared with use of adjuvant placebo. Patients remain in follow-up for the secondary endpoints of distant metastasis-free survival and overall survival.

The dose of 10 mg/kg was chosen based on data from a randomised phase 2 trial[15] that compared various doses of ipilimumab in patients with advanced melanoma, showing the best results with 10 mg/kg. This dose is substantially higher than the approved dose of 3 mg/kg for the treatment of patients with advanced melanoma.[8] The ongoing intergroup trial ECOG 1609 (NCT 01274338) in the USA comparing high-dose interferon treatment with 1 year of treatment with ipilimumab at either 10 mg/kg or 3 mg/kg might provide additional insight as to whether the higher dose of ipilimumab provides additional benefits compared with the standard dose of ipilimumab used for unresectable metastatic disease, and whether either dose of ipilimumab improves outcomes or is less toxic than high-dose interferon.

Recently, several predictive factors for the efficacy of interferon in the adjuvant setting for high-risk melanoma have been identified. In the EORTC 18952 trial, which compared intermediate doses of interferon as adjuvant treatment with observation, and in the EORTC 18991 trial of adjuvant pegylated interferon versus observation, patients were stratified by nodal status: microscopic only (sentinel node-positive) versus macroscopic or palpable, and by the presence of ulceration of the primary.[16–18] The importance of microscopic versus macroscopic nodal involvement and the presence or absence of ulceration of the primary have been clearly shown in a meta-analysis of these two trials in 2644 patients[19] and was confirmed by long-term data—ie, overall survival in the EORTC 18991 trial.[18] Moreover, the overriding importance of ulceration has been shown in an individual patient data meta-analysis of 15 trials of adjuvant interferon versus observation.[11]

We noted similar trends in this trial. Analyses, stratified by stage at randomisation, suggested that patients with microscopic involvement only might have a greater benefit than patients with palpable nodes. But importantly, with ipilimumab, the benefit was still substantial in the latter subgroup, whereas this was not the case in the EORTC interferon trials. Similarly, patients with an ulcerated melanoma seemed to benefit from ipilimumab more than patients with a non-ulcerated primary. By contrast with interferon, the effect of ipilimumab is still substantial in the latter subgroup. When these two important determinants were combined, analyses stratified by stage suggested that the benefit in patients with microscopic nodal involvement with an ulcerated primary appeared greatest, followed by that observed in patients with palpable nodes with an ulcerated primary, or in patients with microscopic nodal involvement and an non-ulcerated primary, whereas in patients with palpable nodes and a non-ulcerated primary the benefit was the lowest (table 3).

In patients with stage IIIA disease with limited microscopic nodal involvement, who, by definition, have a non-ulcerated primary, there was a suggestion of only limited benefit (HR 0·91, 99% CI 0·49–1·68), whereas in those with stage IIIB (HR 0·61, 0·35–1·04) or IIIC (HR 0·42, 0·16–1·12) the effect was important (appendix). These observations suggest that ulcerated melanoma is a separate biological entity, for which a number of additional observations have been reported in terms of stromal components, gene profiling, and immune-suppressed status of associated sentinel nodes.[20–23]

The adverse event profile of ipilimumab in the adjuvant setting is substantial, resulting in around 40% of patients discontinuing treatment by the end of the initial dosing period—ie, before maintenance therapy. This is a higher frequency than has been observed in a pooled analysis of studies with the dose of 10 mg/kg in patients with advanced melanoma.[10] Whether this is due to longer drug exposure, or to a greater sensitivity in stage III disease remains speculative. Most immune-related dermatological, gastrointestinal, and hepatic manifestations resolved within 4–6 weeks, but for endocrinopathies the median time to resolution was 31 weeks, with 59 (44%) of 134 patients remaining on hormone replacement therapies. Of concern are the drug-related fatalities in the ipilimumab group. Effective management of ipilimumab-related immune-related adverse events is complex and requires proactive monitoring, early intervention, and aggressive immunosuppressive management and meticulous instruction of patients. Of note, of the five (1%) patients who died due to drug-related causes after discontinuation of ipilimumab, four received corticosteroids and only one received anti-TNF antibodies; we do not know whether the lack of administration of corticosteroids in one patient and of anti-TNF antibodies in four patients would have changed the outcome.

Adjuvant ipilimumab therapy for patients with high-risk stage III melanoma clearly improves recurrence-free survival. We noted efficacy of the treatment across subgroups including those with high tumour burden. The risk–benefit ratio of adjuvant ipilimumab at this dose and schedule requires additional assessment based on distant metastasis-free survival and overall survival endpoints to define its definitive value.

Contributors

AMME participated in the literature search, study design, and writing the manuscript, and had a major contribution in patient accrual; VC-S and JMR participated in writing the manuscript, and had a major contribution in patient accrual; J-JG and RD participated in the data interpretation and writing the manuscript, and had a major contribution in patient accrual; JDW participated in the study design, data interpretation, writing the manuscript, and had a major contribution in patient accrual; HS and MM

participated in the data collection, data interpretation, and writing the manuscript, and a had major contribution in patient accrual; OH, CR, PAA, CL, MS, and JSW participated in the data collection and data interpretation, and had a major contribution in patient accrual; VF had a major contribution in patient accrual; CK participated in the study design, data collection, medical review of data, data interpretation, and writing the manuscript; AH participated in the literature search, study design, data collection, data interpretation, and writing the manuscript; VdP participated in data collection, data analysis, data interpretation, and writing the manuscript; RKG participated in the data collection, medical review of data, and data interpretation; GdS participated in the data collection and writing the manuscript; SS participated in the study design, data collection, data analysis, data interpretation, and writing the manuscript; AT participated in the study design, data collection, and writing the manuscript and had a major contribution in patient accrual.

Declaration of interests

AMME has received personal fees from Bristol-Myers Squibb, Amgen, Merck, and MedImmune for serving on an advisory board, and personal fee from GlaxoSmithKline for serving on a data and safety monitoring board; VCS has received personal fees from Bristol-Myers Squibb, GlaxoSmithKline, Roche, Merck, and Amgen for serving on an advisory board; J-JG has received personal fees and non-financial support from Bristol-Myers Squibb, Roche, GlaxoSmithKline, Merck, and Novartis for serving on an advisory board, lecturer, travel support, and grants from Bristol-Myers Squibb and GlaxoSmithKline; RD has received personal fees from Bristol-Myers Squibb, MSD, Roche, GlaxoSmithKline, and Novartis for serving on an advisory board; JDW has received other fees from Bristol-Myers Squibb, MSD, and MedImmune for serving as a consultant, and a grant from Bristol-Myers Squibb; HR has received personal fees from Bristol-Myers Squibb for consulting and lecturing, from GlaxoSmithKline for lecturing and serving on an advisory board, and from GlaxoSmithKline for lecturing; OH has received personal fees from Bristol-Myers Squibb for lecturing and grants from Bristol-Myers Squibb; CR has received other fees from GlaxoSmithKline, Roche, Merck, Bristol-Myers Squibb, and Amgen for serving as a consultant; PA has received personal fees from Bristol-Myers Squibb, Roche, Merck, GlaxoSmithKline, Ventana, Novartis, and Amgen for serving on an advisory board, and grants from Bristol-Myers Squibb, Roche, and Ventana; CL has received personal fees from Bristol-Myers Squibb, GlaxoSmithKline, Roche, Merck, Amgen, and Novartis for serving on an advisory board; MS has received personal fees from Bristol-Myers Squibb and Roche as honoraria and from Merck, Bristol-Myers Squibb, Roche, and GlaxoSmithKline for serving on an advisory board; JSW has received personal fees and grants from Bristol-Myers Squibb; MM has received personal fees from Bristol-Myers Squibb, Roche, MedImmune, and GlaxoSmithKline for serving on an advisory board and lecturing, and grants from Bristol-Myers Squibb and MedImmune; and CK and VdP are employees and shareholders of Bristol-Myers Squibb. JMR, VF, AH, RKG, GdS, SS, and AT have nothing to disclose.

Acknowledgments

This trial was funded by Bristol-Myers Squibb. We thank all EORTC Headquarters team members who have not been included among the co-author list of this publication, and who contributed to the study success: Isabelle Blangenois, Sandra Collette, Valérie Dewaste, Thierry Gorlia, Sven Janssen, Niels Lema, Larissa Polders, Simon Vanderschaeghe; and members of the Bristol-Myers Squibb team, in particular Chantal Lejeune.

References

1 Eggermont AMM, Spatz A, Robert C. Cutaneous melanoma. *Lancet* 2014; **383:** 816–27.

2 Balch CM, Gershenwald JE, Soong S-J, et al. Final version of 2009 AJCC melanoma staging and classification. *J Clin Oncol* 2009; **27:** 6199–206.

3 Balch CM, Gershenwald JE, Soong S-J, et al. Multivariate analysis of prognostic factors among 2313 patients with stage III melanoma: comparison of nodal micrometastases versus macrometastases. *J Clin Oncol* 2010; **28:** 2452–59.

4 Romano E, Scordo M, Dusza SW, Coit DG, Chapman PB. Site and timing of first relapse in stage III melanoma patients: Implications for follow-up guidelines. *J Clin Oncol* 2010; **28:** 3042–47.

5 van Akkooi ACJ, Nowecki ZI, Voit C, et al. Sentinel node tumor burden according to the Rotterdam criteria is the most important prognostic factor for survival in melanoma patients: a multicenter study in 388 patients with positive sentinel nodes. *Ann Surg* 2008; **248:** 949–55.

6 van der Ploeg APT, van Akkooi ACJ, Rutkowski P, et al. Prognosis in patients with sentinel node-positive melanoma is accurately defined by the combined Rotterdam tumor load and Dewar topography criteria. *J Clin Oncol* 2011; **29:** 2206–14.

7 van der Ploeg AP, van Akkooi AC, Haydu LE, et al. The prognostic significance of sentinel node tumour burden in melanoma patients: An international, multicenter study of 1539 sentinel node-positive melanoma patients. *Eur J Cancer* 2014; **50:** 111–20.

8 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.

9 Robert C, Thomas L, Bondarenko I, et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. *N Engl J Med* 2011; **364:** 2517–26.

10 Lebbé C, Weber JS, Maio M, et al. Survival follow-up and ipilimumab retreatment for patients with advanced melanoma who received ipilimumab in prior phase II studies. *Ann Oncol* 2014; **25:** 2277–84.

11 Suciu S, Ives N, Eggermont AM, et al. Predictive importance of ulceration on the efficacy of adjuvant interferon-a (IFN): An individual patient data (IPD) meta-analysis of 15 randomized trials in more than 7,500 melanoma patients (pts). *Proc Am Soc Clin Oncol* 2014; **32** (suppl): (abstr) 9067.

12 Wheatley K, Ives N, Hancock B, Gore M, Eggermont A, Suciu S. Does adjuvant interferon-alpha for high-risk melanoma provide a worthwhile benefit? A meta-analysis of the randomised trials. *Cancer Treat Rev* 2003; **29:** 241–52.

13 Mocellin S, Pasquali S, Rossi CR, Nitti D. Interferon alpha adjuvant therapy in patients with high-risk melanoma: a systematic review and meta-analysis. *J Natl Cancer Inst* 2010; **102:** 493–501.

14 Pocock SJ, Simon R. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. *Biometrics* 1975; **31:** 103–115.

15 Wolchok JD, Neyns B, Linette G, et al. Ipilimumab monotherapy in patients with pretreated advanced melanoma: a randomised, double-blind, multicentre, phase 2, dose-ranging study. *Lancet Oncol* 2010; **11:** 155–64.

16 Eggermont AMM, Suciu S, MacKie R, et al. Post-surgery adjuvant therapy with intermediate doses of interferon alfa 2b versus observation in patients with stage IIb/III melanoma (EORTC 18952): randomised controlled trial. *Lancet* 2005; **366:** 1189–96.

17 Eggermont AMM, Suciu S, Santinami M, et al. Adjuvant therapy with pegylated interferon alfa-2b versus observation alone in resected stage III melanoma: final results of EORTC 18991, a randomised phase III trial. *Lancet* 2008; **372:** 117–26.

18 Eggermont AM, Suciu S, Testori A, et al. Long term results of the randomized phase III trial EORTC 18991 of adjuvant therapy with pegylated interferon alfa-2b versus observation in resected stage III melanoma. *J Clin Oncol* 2012; **30:** 3810–18.

19 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.

20 Spatz A, Cook MG, Elder DE, Piepkorn M, Ruiter DJ, Barnhill RL. Interobserver reproducibility of ulceration assessment in primary cutaneous melanomas. *Eur J Cancer* 2003; **39:** 1861–65.

21 Winnepenninckx V, Lazar V, Michiels S, et al. Gene expression profiling of primary cutaneous melanoma and clinical outcome. *J Natl Cancer Inst* 2006; **98:** 472–82.

22 Elliott B, Scolyer RA, Suciu S, et al. Long-term protective effect of mature DC-LAMP+ dendritic cell accumulation in sentinel lymph nodes containing micrometastatic melanoma. *Clin Cancer Res* 2007; **13:** 3825–30.

23 Eggermont AM, Spatz A, Lazar V, Robert C. Is ulceration in cutaneous melanoma just a prognostic and predictive factor or is ulcerated melanoma a distinct biologic entity? *Curr Opin Oncol* 2012; **24:** 137–40.