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Original Research

Adjuvant ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results of the European Organisation for Research and Treatment of Cancer 18071 double-blind phase 3 randomised trial

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KEYWORDS
Ipilimumab;
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Long-term results

Abstract ***Background:*** Since 2015, adjuvant therapy with ipilimumab is an approved treatment for stage III melanoma based on a significantly prolonged recurrence-free survival (RFS). At a median follow-up of 5.3 years, RFS, distant metastasis-free survival (DMFS) and overall survival (OS) were each significantly prolonged in the ipilimumab group compared with the placebo group, despite a 53.3% (ipilimumab) versus 4.6% (placebo) treatment discontinuation rate due to adverse events. We present now long-term follow-up results of this European Organisation for Research and Treatment of Cancer 18071 trial.
Patients, methods and results: A total of 99 sites randomised 951 patients with stage III cutaneous melanoma (excluding lymph node metastasis $\leq$1 mm or in-transit metastasis) with adequate resection of lymph nodes to receive intravenous infusions of ipilimumab 10 mg/kg or placebo, every 3 weeks for 4 doses, then every 3 months for up to 3 years. The RFS, DMFS and OS, as reported by the local investigators, were assessed by the intention-to-treat analysis. Among 431 patients randomised at 63 sites and who were still alive at the analysis reported in 2016, recent follow-up information could be obtained for 264 patients. The median OS follow-up was 6.9 years. The RFS (hazard ratio [HR] 0.75, 95% confidence interval 0.63–0.88; P < 0.001), DMFS (HR 0.76, 0.64–0.90; P = 0.002) and OS (HR 0.73, 0.60–0.89; P = 0.002) benefit observed in the ipilimumab group was durable with an 8.7% absolute difference at 7 years for OS. The benefit was consistent across subgroups.
Conclusions: Adjuvant therapy with ipilimumab prolongs RFS, DMFS and OS significantly. The benefit is sustained long term and consistent across subgroups.

1. Introduction

After the era of adjuvant interferon (IFN) therapies, having marginal impact on outcomes of patients with stage II-III melanoma, which were approved between 1996 and 2009 by the US Food and Drug Administration (FDA) (high-dose IFN and pegylated IFN) and European Medicine Agency (EMA) (high-dose and low-dose IFN), we have entered a new era of effective therapies for both advanced disease [1,2] and the adjuvant setting [3–7]. With the effective treatments previously approved for advanced melanoma [2], we have witnessed within a time span of only 4 years (2015–2018) the results of 4 randomised controlled trials demonstrating a significant impact on recurrence-free survival (RFS), followed by approval by the regulatory agencies. Prolonged RFS has been reported for adjuvant therapy with ipilimumab [3], nivolumab [4], dabrafenib plus trametinib [5] and pembrolizumab [6]. Mature data demonstrating a significant impact on overall survival (OS) have been reported for ipilimumab [7]. Approval for ipilimumab (FDA 2015) and nivolumab (FDA 2017, EMA 2018) was followed by approval for dabrafenib plus trametinib (FDA and EMA 2018) and pembrolizumab (EMA 2018, FDA 2019).

We previously reported the primary results of the European Organisation for Research and Treatment of Cancer (EORTC) 18071 phase 3 trial with adjuvant ipilimumab versus placebo in patients with resected stage III melanoma [3]. At a median follow-up (FU) time of 2.7 years, adjuvant ipilimumab significantly improved RFS, the primary end-point, compared with placebo (hazard ratio [HR]: 0.75; p = 0.0013). Subsequently, at a median FU time of 5.3 years, RFS (HR: 0.76), distant metastasis-free survival (DMFS) (HR: 0.76) and OS (HR: 0.73) were each significantly prolonged in the ipilimumab group compared with the placebo group, despite a 53.3% (ipilimumab) versus 4.6% (placebo) treatment discontinuation rate due to adverse events [7]. The global health status score, primary health-related quality of life end-point, was not affected by ipilimumab [8].

Here, we report on the long-term FU results on OS, and also on RFS and DMFS, based on the local investigator assessment, for the first adjuvant randomised controlled trial, EORTC 18071, of ipilimumab in high-risk patients with stage III cutaneous melanoma after having undergone a complete regional lymph node dissection.

2. Patients and methods

2.1. Patients

Eligible patients were those aged 18 years or older with histologically confirmed cutaneous melanoma metastatic to regional lymph nodes. According to the 2009 American Joint Committee on Cancer classification, eligible patients had either stage IIIA melanoma (at least one micrometastasis measuring >1 mm in the greatest diameter, according to the Rotterdam Criteria of sentinel node [SN] tumour load), stage IIIB or stage IIIC melanoma, with no in-transit metastases [9–11].

Complete regional lymphadenectomy was required within 12 weeks before randomisation. The exclusion criteria included Eastern Cooperative Oncology Group performance status greater than 1, autoimmune disease, uncontrolled infections, significant cardiovascular disease (New York Heart Association (NYHA) grade III or IV), lactate dehydrogenase levels > 2x the upper limit of normal, use of systemic corticosteroids and prior systemic therapy for melanoma.

The protocol was approved by the EORTC protocol review committee and independent ethics committees. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and with good clinical practice as defined by the International Conference on Harmonisation. All participating patients gave written informed consent.

2.2. Study design and treatment

In this randomised double-blind phase 3 study, patients were enrolled from 99 centres in 19 countries. Registration was done centrally at the EORTC headquarters. Randomisation was stratified by 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 region (North America, European countries and Australia), using a minimisation technique. The unblinded local pharmacist performed the randomisation. Clinical investigators and those collecting the data were blinded to treatment group assignment. The patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of ipilimumab 10 mg/kg or placebo every 3 weeks for 4 doses, then every 3 months for up to 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or withdrawal of consent (Supplementary Fig. 1).

The primary end-point was RFS, and secondary end-points included OS, DMFS, safety and health-related quality of life.

2.3. Assessments

Patients in both treatment groups were assessed for recurrence and distant metastases every 3 months during the first 3 years and every 6 months thereafter. Physical examination, chest radiography, computed tomography or magnetic resonance imaging (MRI) and/or other imaging techniques were performed if indicated. Recurrence or metastatic lesions had to be histologically confirmed whenever possible. The first date when recurrence was observed was taken into account, regardless of the method of assessment. The local investigator assessments of first recurrence and first distant metastasis were considered for this long-term evaluation of the outcome.

RFS was defined as the time from randomisation until the date of first recurrence (local, regional or distant metastasis) or death from any cause. DMFS was defined as the time from randomisation until the date of first distant metastasis or death from any cause. OS was defined as the time from randomisation until death from any cause. The last FU date was used to censor the RFS and DMFS for patients still alive and without disease recurrence and distant metastases, respectively, and OS for patients still alive.

Until the beginning of 2016, an independent data and safety monitoring board monitored the overall conduct of the study and reviewed the safety data and the efficacy data. In addition, an independent review committee (IRC), blinded to study group assignments, assessed disease status and the date of recurrence.

2.4. Statistical analysis

In this study, a total of 99 sites randomised 951 patients. The final analysis for the primary end-point (RFS based on the IRC assessment) was performed based on 528 RFS events allowing detection of a treatment HR of 0.75 (2-sided $\alpha = 5\%$) with >90% power [3]. Subsequently, based on 506 DMFS events (IRC reviewed) and 376 deaths reported at the clinical cut-off date (31st January 2016), DMFS and OS final analyses were performed simultaneously [7] (see also Supplementary statistical considerations).

A total of 63 sites agreed to participate in the long-term FU phase, initially planned in the protocol. Among 431 patients randomised by these sites and who were still alive at the analysis reported in 2016, recent FU information could be obtained for 264 patients as not all sites could provide such information and not all patients consented to participate. The database was locked in January 2019.

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 carried out using a log-rank test stratified by stage at randomisation, at the 2-sided alpha level of 5%. The Cox proportional hazards model stratified by stage as provided at randomisation was used to estimate the HR for RFS, DMFS and OS in the ipilimumab group compared with the placebo group and the corresponding 95% CI.

For exploratory purposes, we investigated the predictive importance of several factors regarding the efficacy outcomes. Forest plots were produced, and the interactions between each variable and the treatment group in a Cox model were indicated. For subgroup analyses, the HRs were plotted along with their 99% CIs.

The analyses of the efficacy end-points were performed on all patients randomised, using the intention-to-treat principle.

All analyses were performed using SAS software version 9.4 (SAS Institute, Cary, NC).

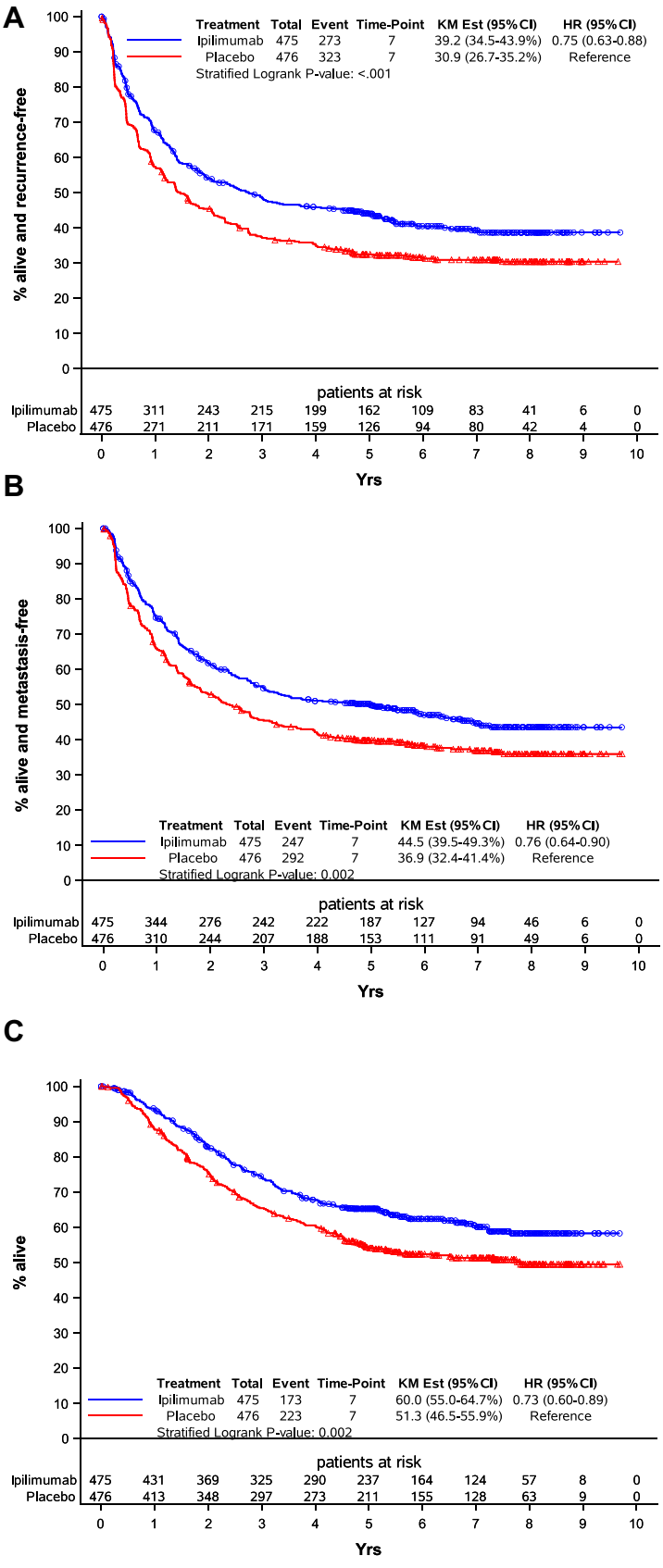

Fig. 1. **Treatment comparison regarding (A) recurrence-free survival; (B) distant metastasis-free survival and (C) overall survival**. Kaplan–Meier (KM) curves, along with a 7-year KM rate estimate (Est) and its 95% confidence interval (CI), and the estimated hazard ratio (HR) stratified by stage provided at randomisation and its 95% CI.

3. Results

The median FU was 6.9 years (interquartile range: 5.2–7.9) among all patients, 6.6 years (interquartile range: 5.0–7.8) in the ipilimumab group and 7.1 years (interquartile range: 5.3–8.1) in the placebo group.

3.1. Recurrence-free survival

In this long-term FU analysis, there were 596 RFS events reported: 273 (57.5%) of 475 patients in the ipilimumab group and 323 (67.9%) of 476 patients in the placebo group. The distribution of the type of the first RFS event in the ipilimumab and placebo groups was locoregional recurrence only (17.9% vs 21.6%), distant metastasis (36.9% vs 45.0%) and death without recurrence (2.7% vs 1.3%) (Supplementary Fig. 2). The RFS remained significantly longer for the ipilimumab group compared with placebo (HR, stratified by stage, 0.75, 95% CI: 0.63–0.88; $P < 0.001$), and the 7-year RFS rate was higher in the ipilimumab group compared with the placebo group: 39.2% (95% CI: 34.5–43.9) and 30.9% (95% CI: 26.7–35.2), respectively (Fig. 1A).

The improvement in RFS due to adjuvant ipilimumab was consistent across subgroups (Fig. 2A). The impact of ipilimumab on RFS was similar in men and

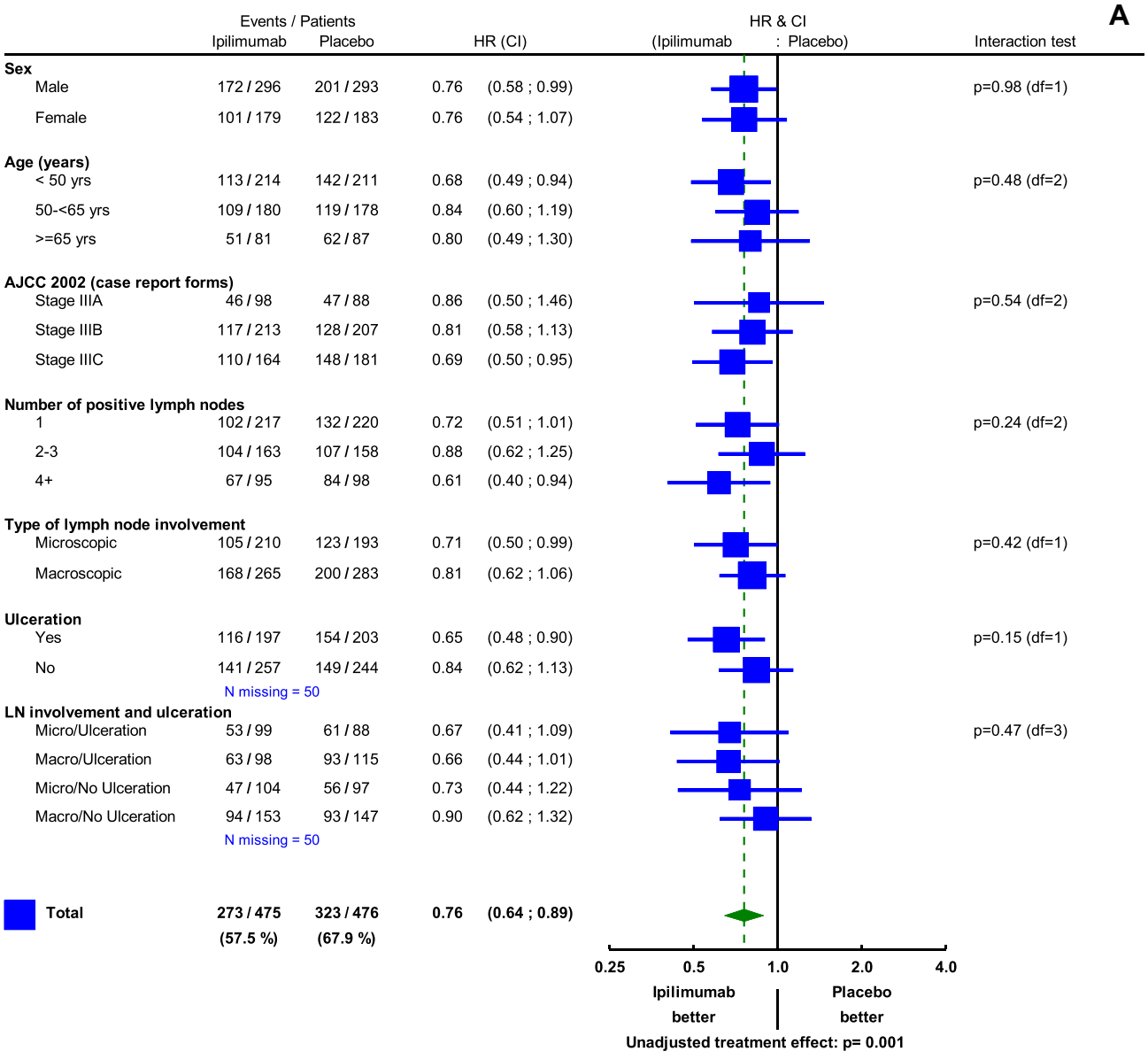

Fig. 2. **Forest plot according to the treatment group for (A) RFS and (B) OS**. The results are expressed as unstratified hazard ratios (HRs) for the risk of recurrence or death (panel A) or of death (panel B) in the ipilimumab group compared with the placebo group, with 95% confidence interval (CI) and 99% CI for the overall group and each subgroup comparison, respectively. RFS, recurrence-free survival; OS, overall survival. AJCC, American Joint Committee for Cancer; LN, lymh node.

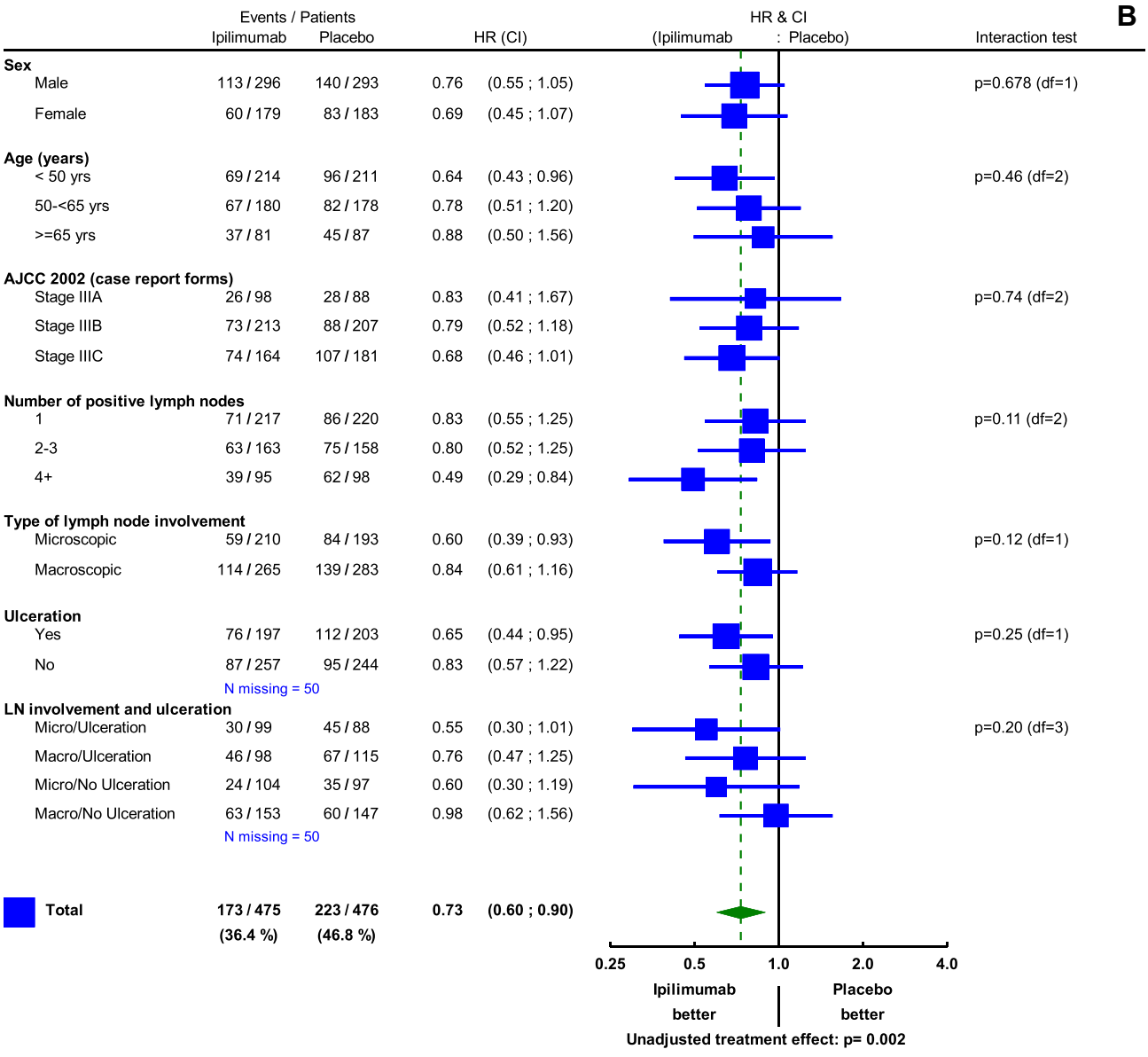

Fig. 2. (*continued*).

women (HR: 0.76, in both groups) and in patients with a microscopic (HR: 0.71) and macroscopic involvement (HR: 0.81). Numerically, the observed treatment effect was higher in patients with ulcerated melanoma (HR: 0.65, 99% CI: 0.48–0.90) than in those with non-ulcerated melanoma (HR: 0.84, 99% CI: 0.62–1.13) (test for interaction: P = 0.15).

Additional exploratory subgroup analyses in patients with a microscopic and macroscopic involvement are provided in Supplementary Fig. 3.

3.2. Postprotocol treatment and OS after an RFS event

In the ipilimumab group, among the 273 patients who had an RFS event, 221 received at least one subsequent treatment (Table 1). These included ipilimumab (n = 26), anti–programmed death receptor - 1 (PD-1) therapy (n = 31), and a BRAF inhibitor (n = 70). In the placebo group, among the 323 patients who had an RFS event, 282 received subsequent treatment: ipilimumab (n = 82), anti-PD-1 therapy (n = 41) and a BRAF inhibitor (n = 89). OS after an RFS event was similar in the two treatment groups (HR: 0.90), the 7-year estimate being approximately 30% in each group (Fig. 3). This suggests that the treatment difference in terms of RFS would persist in terms of OS. OS after recurrence was also similar in the two treatment groups (HR: 0.86) (Supplementary Fig. 4).

3.3. Distant metastasis-free survival

There were 539 DMFS events reported: 247 (52.0%) patients in the ipilimumab group and 292 (61.3%) patients in the placebo group. In the ipilimumab and

Table 1
Postprotocol treatment in patients who had a disease recurrence or died.

Type of treatment	Ipilimumab (N = 273) N (%)	Placebo (N = 323) N (%)
Any second-line treatment reported	221 (81.0)	282 (87.3)
Chemotherapy	85 (31.1)	105 (32.5)
Radiotherapy	42 (15.4)	62 (19.2)
Surgery	108 (39.6)	117 (36.2)
Interferon	18 (6.6)	33 (10.2)
Interleukin	21 (7.7)	27 (8.4)
Ipilimumab	26 (9.5)	82 (25.4)
BRAF inhibitor	70 (25.6)	89 (27.6)
MEK inhibitor	24 (8.8)	33 (10.2)
Anti–programmed cell death receptor 1 (PD-1)	31 (11.4)	41 (12.7)
Vaccination	10 (3.7)	18 (5.6)

placebo groups, there were 233 (49.1%) and 283 (59.5%) patients who developed distant metastases, respectively, and 14 (2.9%) and 9 (1.9%) patients who died without documented distant metastases, respectively (Supplementary Table 1). DMFS was significantly longer in the ipilimumab group compared with the placebo group (HR, stratified by stage, 0.76, 95% CI: 0.64–0.90; P = 0.002), and the 7-year DMFS rate was higher in the ipilimumab group compared with the placebo group: 44.5% (95% CI: 39.5–49.3) vs 36.9% (95% CI: 32.4–41.4) (Fig. 1B).

Subgroup analyses for DMFS by the treatment group showed similar results to those for RFS (Supplementary Fig. 5). Additional exploratory subgroup analyses in patients with a microscopic and macroscopic involvement are provided in Supplementary Fig. 5.

3.4. Overall survival

There were 396 deaths reported: 173 in the ipilimumab group and 223 in the placebo group. OS was significantly longer for ipilimumab compared with placebo (HR, stratified by stage, 0.73; 95% CI: 0.60–0.89; P = 0.002) (Fig. 1C). The 7-year OS rate was 60.0% (95% CI: 55.0–64.7) in the ipilimumab group and 51.3% (95% CI: 46.5–55.9) in the placebo group. The OS curves flattened at the end of the FU, suggesting a long-term survival of these patients.

The improvement in OS with ipilimumab was generally consistent across subgroups (Fig. 2B). It was similar in men (HR: 0.76) and in women (HR: 0.69), in patients with microscopic involvement (HR: 0.60, 99% CI: 0.39–0.93) and in those with macroscopic involvement (HR: 0.84, 99% CI: 0.61–1.16) (test for interaction: P = 0.12). Interestingly, the treatment effect was possibly more pronounced in patients with 4 or more positive lymph nodes (HR: 0.49, 0.29–0.84) than those with one (HR: 0.83, 0.55–1.25) or two to three positive lymph nodes (HR: 0.80, 0.52–1.25) (test for interaction: P = 0.11).

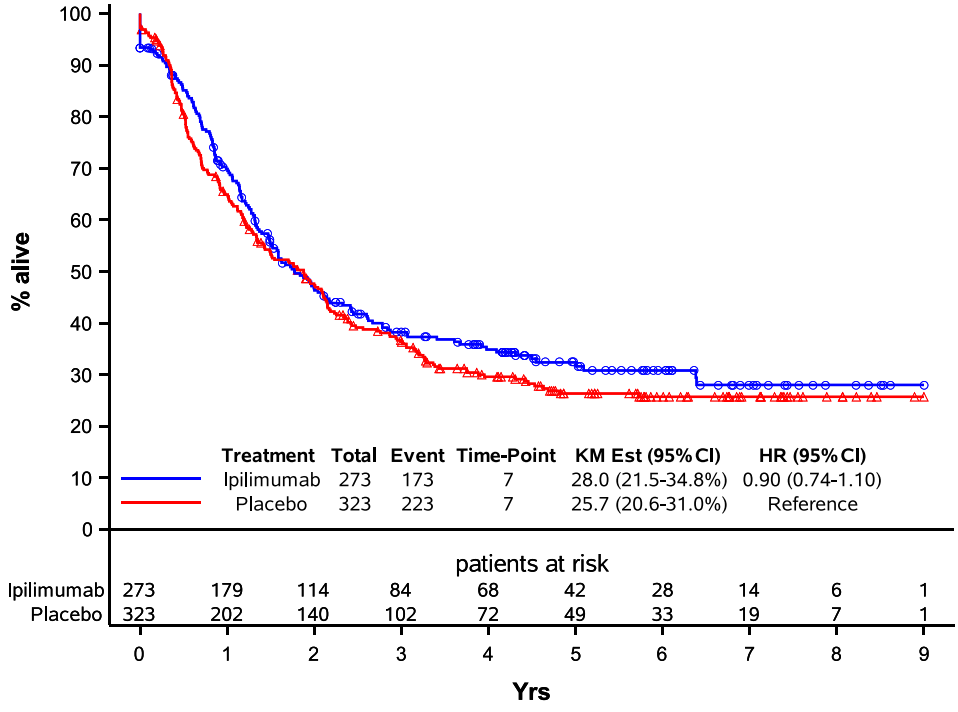

Fig. 3. **OS from the first RFS event by the treatment group**. Kaplan–Meier (KM) curves, along with a 7-year KM rate estimate (Est) and its 95% confidence interval (CI), and ipilimumab vs placebo hazard ratio (HR) for the risk of death and its 95% CI. RFS, recurrence-free survival; OS, overall survival.

We further explored to see whether the high number of positive lymph nodes was associated with a greater treatment benefit in the two main subgroups of patients: those with a microscopic and those with a macroscopic lymph node involvement. In patients with a macroscopic lymph node involvement, the number of lymph nodes could be of predictive importance (test for interaction: P = 0.03). The higher the number of positive lymph nodes, the greater the treatment benefit; the HR was 0.52 (99% CI: 0.28–0.94) among patients with 4 or more positive lymph nodes, but 1.18 (99% CI: 0.69–2.00) among patients with only one positive lymph node (Supplementary Fig. 6).

In patients with a microscopic involvement, the estimated treatment impact was lower in stage IIIA patients—who had the best prognosis—(HR: 0.83, 99% CI: 0.41–1.67) than in stage IIIB patients (HR: 0.49, 99% CI: 0.25–0.94) and in stage IIIC patients (HR: 0.42, 99% CI: 0.14–1.26) (interaction test: P = 0.26) (Supplementary Fig. 6).

Ipilimumab prolonged OS in patients with ulcerated melanoma (HR: 0.65, 99% CI: 0.44–0.95) (Fig. 2B). Patients without ulcerated melanoma seemed to benefit from the treatment as well (HR: 0.83, 99% CI: 0.57–1.22) (test for interaction: P = 0.25). In patients with microscopic involvement, the observed ipilimumab effect on OS was similar in patients with ulcerated melanoma (HR: 0.54, 99% CI: 0.30–1.00) and in those without ulcerated melanoma (HR: 0.59, 99% CI: 0.30–1.17), whereas in those with macroscopic involvement, the observed effect was moderate in those with ulcerated melanoma (HR: 0.77, 99% CI: 0.47–1.26) and minimal in those with non-ulcerated melanoma (HR: 0.97, 99% CI: 0.61–1.54) (test for interaction: P = 0.38).

4. Discussion

We demonstrated here that adjuvant therapy with ipilimumab prolongs RFS, DMFS and OS significantly in patients with resected stage III melanoma. The benefit is sustained long term and consistent across subgroups despite a discontinuation rate of 53.4% with ipilimumab therapy. Importantly, we observed that the duration of OS after recurrence was comparable in ipilimumab-treated and placebo patients, supporting the interpretation that the beneficial effect of adjuvant ipilimumab therapy was obtained by its administration starting within 3 months after surgery. However, there was no complete crossover after recurrence in the placebo-treated patients. Only 25% of patients from the placebo arm received ipilimumab after the diagnosis of recurrence. In addition, with a long-term follow-up, the estimated OS benefit was highest in patients with an ulcerated primary (HR: 0.65), and a small benefit in patients with a non-ulcerated primary was maintained (HR: 0.83). This is in contrast with the findings of the adjuvant IFN EORTC 18952 and 18991 trials [12–16] and of the meta-analysis of 15 IFN trials [17], where the benefit was purely restricted to patients with an ulcerated primary. In the more recent anti–PD-1 trials and the COMBI-AD trial, such a selective benefit in the ulcerated patient population was not observed [4–6].

The adjuvant therapy with the high dose 10 mg/kg as used in the EORTC 18071 trial was associated with increased toxicity, as indicated by a 53% discontinuation rate due to adverse events. This is much higher than the 26% discontinuation rate observed in the COMBI-AD trial [5]. Lower discontinuation rates have been observed in the anti–PD-1 trials with nivolumab (Checkmate-238) and with pembrolizumab (EORTC 1325—KN054) [4,6]. The Intergroup trial has reported similar efficacy results for the 3 mg/kg and 10 mg/kg doses, but with a lower discontinuation rate in the former group (35%) [18]. However, ipilimumab is no longer considered a prime candidate for adjuvant therapy because of this toxicity and because adjuvant therapy with nivolumab has been demonstrated to lead to superior outcomes [4].

The importance of this communication is the observed long-term sustained effect of ipilimumab on RFS and OS. The surrogacy of RFS for OS has already been reported in adjuvant trials conducted in the pre-new drug era [19]. However, during that period, the 2-year rate of OS after an RFS event was 27% [19], far lower than the one reported in the pembrolizumab (58.0%) and ipilimumab (44.7%) arms of the KEYNOTE-006 randomised trial [20]. Long-term FU is required to assess the extent to which the impact of anti–PD-1 [6] and COMBI-AD [5] vs placebo on RFS observed in the adjuvant trials will be maintained and translated in an OS difference.

Recently, the American Joint Committee of Cancer (AJCC)-8 staging system has been introduced [21]. The conclusions of all the recent adjuvant trials in stage III patients, all using the AJCC-7 staging system, are unlikely to be changed by using the recently introduced AJCC-8 staging system, as suggested by the comparative study of AJCC-7 versus AJCC-8 staging regarding their prognostic and predictive value in the EORTC 1325 adjuvant trial [22].

Whether all SN-positive patients should first undergo a completion lymph node dissection (CLND) before being candidates for adjuvant therapy with the new anti–PD-1 treatments, irrespective of their BRAF mutation status, or the combination of dabrafenib/trametinib, for patients with BRAF-mutant melanoma, is a point of debate because all trials of these drugs were conducted in patients after full regional nodal clearance. The outcomes of the dermatologic cooperative oncology group (DECOG) and the multicenter selective lymphadenectomy trial II (MSLT-II) trials have demonstrated that CLND does not improve outcome in SN-positive

patients [23,24]. It would therefore be logical to conclude that CLND is no longer obligatory for a decision to propose adjuvant therapy [25,26]. Moreover, simplified staging requirements may be achieved by incorporating ulceration status of the primary melanoma into the decision-making [27].

The new revolution that will have a major impact on the management of patients with melanoma will be the use of neoadjuvant therapy [28]. This may be true for BRAF/MEK inhibitor combination therapy in stage III patients [29], but the expectations are clearly the highest with the combination of anti–PD-1 and anti-cytotoxic T-lymphocyte associated-protein 4 (CTLA4) as demonstrated in patients with palpable nodal stage III disease [30]. Two cycles of nivolumab plus low-dose ipilimumab have been reported to induce up to 70% pathologic complete responses, indicating that in the near future, we may be able to avoid disfiguring lymph nodal dissections in a majority of patients with stage III melanoma.

In conclusion, long-term benefit is achieved with adjuvant ipilimumab therapy in stage III melanoma. This observation enhances the likelihood of even more prominent long-term benefits with the more recently approved adjuvant treatment regiments with anti–PD-1 and BRAF/MEK inhibition combination therapy and will bring us into the next era of neoadjuvant therapies that will revolutionise management of patients with stage III melanoma and is likely to reduce surgery to minimally invasive diagnostic procedures in most patients.

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Conflict of interest statement

A.M.M.E. received personal fees as a consultant advisor for Actelion, Agenus, Amgen, Bayer, Bristol-Myers Squibb (BMS), Catalym, Celldex, Gilead, GlaxoSmithKline (GSK), HalioDx, Incyte, IO Biotech, ISA Pharmaceuticals, MedImmune, Merck Sharp & Dohme (MSD), Nektar, Novartis, Pfizer, Polynoma, Regeneron, Sanofi and SkylineDx. He has equity in RiverDx, SkylineDx and Theranovir. V.C.-S. received personal fees as a consultant advisor for Amgen, BMS, GSK, MSD and Roche. J.-J.G. received personal fees as a consultant advisor and lecturer for BMS, GSK, MSD, Novartis and Roche. R.D. received personal fees as a consultant advisor for BMS, GSK, MSD, Novartis and Roche and grant support from BMS. J.D.W. received personal fees as a consultant advisor for Adaptive Biotech, Advaxis, Amgen, Apricity, Array BioPharma, Ascentage Pharma, Astellas, Bayer, BeiGene, BMS, Celgene, Chugai, Elucida, Eli Lilly, F-star, Genentech, Imvaq, Janssen, Kleo Pharma, Linneaus, MedImmune, Merck, Neon Therapeutics, Ono, Polaris Pharma, Polynoma, PsiOxus, Puretech, Recepta, Trieza, Sellas Life Sciences, Serametrix, Surface Oncology and Syndax, honorarium from Esanex and research support from BMS, MedImmune, Merck Pharmaceuticals and Genentech. He has equity in Potenza Therapeutics, Tizona Pharmaceuticals, Adaptive Biotechnologies, Elucida, Imvaq, BeiGene, Trieza and Linneaus. H.S. received personal fees as a consultant advisor and lecturer for BMS, Novartis, MSD and Roche and grant support from MSD. O.H. has received personal fees as a lecturer for BMS and a grant support from BMS. C.R. received personal fees as a consultant advisor for Amgen, BMS, GSK, MSD, Novartis, Pierre Fabre and Roche. P.A.A. received personal fees as a consultant advisor for Array, AstraZeneca, BMS, Genmab, Idera, Immunocore, Incyte, MedImmune, Merck Serono, MSD, NewLink Genetics, Novartis, Pierre Fabre and Roche - Genentech, Sanofi, Syndax, Sandoz, Sun Pharma and 4SC, travel support from MSD and research funding from Array, Bristol-Myers Squibb and Roche-Genentech. C.L. received personal fees as a consultant advisor for Amgen, BMS, GSK, Novartis and Roche. M.S. received honoraria from BMS and Roche and personal fees as a consultant advisor for Amgen, BMS, GSK, MSD and Roche. J.S.W. received personal fees as a consultant advisor for BMS. M.M. received personal fees as a consultant advisor and lecturer for BMS, GSK, MedImmune and Roche. F.H. and V.d.P. are employees and shareholders of BMS. J.M.R., V.F., M.K., S.S. and A.T. declared no competing interests.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.001.

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