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## Original Research

# Indirect treatment comparison of nivolumab versus placebo for the adjuvant treatment of melanoma

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## KEYWORDS

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**Abstract** *Introduction:* Until recently, adjuvant treatment options for stage III and IV resectable melanoma have been limited. Patients were often managed through routine surveillance. The phase III randomised controlled trial (RCT) CheckMate 238 (238) demonstrated the safety and efficacy of nivolumab as an adjuvant treatment for melanoma in patients with stage IIIB/C or IV disease (American Joint Committee on Cancer [AJCC], 7th edition) versus ipilimumab. The study objective was to estimate the relative efficacy, safety and health-related quality of life (HRQoL) between nivolumab and routine surveillance.

**Methods:** Indirect treatment comparisons (ITCs) of nivolumab versus placebo were constructed using data from 238 and EORTC 18071. EORTC 18071 is a phase III RCT comparing ipilimumab with placebo in patients with resected stage IIIA–IIIC melanoma (AJCC, 6th edition). ITCs were performed using the Bucher comparison method and patient-level data for efficacy, safety and HRQoL.

**Results:** For the efficacy outcomes, nivolumab performed significantly better than placebo for recurrence-free survival (hazard ratio [HR]: 0.53 [95% confidence interval {CI}: 0.41, 0.68]) and distant metastases-free survival (HR: 0.59 [95% CI: 0.44, 0.78]). Safety ITCs indicated that patients receiving nivolumab had a greater hazard of experiencing an adverse event (AE) and AEs leading to treatment discontinuation, whereas there was a non-significant increased hazard of experiencing a serious AE. HRQoL ITCs showed comparable time to deterioration in 14 of the 15 QLQ-C30 domains; only the dyspnoea domain significantly favoured placebo.

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**Conclusion:** Nivolumab was associated with significantly improved efficacy outcomes versus placebo, whereas maintaining patient's overall HRQoL. Across the different analysis and populations, there was a high level of consistency in the effect size.

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## 1. Introduction

Melanoma is an aggressive skin cancer that has increased in prevalence since the 1990s [1,2]. This rising incidence is widely attributed to changing lifestyle factors such as increases in voluntary sun exposure and the use of ultraviolet sunbeds, which increase people's exposure to ultraviolet light [3,4]. The global incidence of melanoma in 2015 was 351,880 cases (95% confidence interval [CI]: 281,633, 445,036) with an age-standardised rate of five cases per 100,000 persons (95% CI: 4, 7) [5]. It has been estimated that cutaneous melanoma results in 55,000 deaths annually [6]. Kanaki *et al.* calculated 5- and 10-year melanoma-specific survival rates for patients stratified by stage (based on American Joint Committee on Cancer [AJCC], 7th edition) [7,8], showing an increasing mortality risk with disease stage (82% and 64% for stage IIIA, 64% and 54% for stage IIIB, 46% and 34% for stage IIIC disease and 40% and 35% for stage IV, respectively).

In the past few years, treatment options for patients with completely resected melanoma at high risk of recurrence have been limited. Interferon alpha has been available in the United States of America (USA) and in Europe; however, its use has been limited by its modest survival benefit and toxicity profile [9–11]. Ipilimumab was also used in the USA based on evidence from study EORTC 18071, which demonstrated significantly improved recurrence-free survival (RFS), distant metastasis-free survival (DMFS) and overall survival (OS) versus placebo [12]. Until the recent approval of nivolumab, pembrolizumab and dabrafenib in combination with trametinib, patients were primarily managed through routine surveillance [10]. The lack of adjuvant treatments meant that patients with resected macroscopic lymph node involvement or metastatic disease remained at high risk of relapse and death after complete resection. Without active treatment, only about one-third of patients with stage III melanoma are cured with surgery alone [13]. For the other two-third of patients, relapse can have a profound impact on their survival and quality of life [14,15].

Nivolumab, a humanised IgG4 anti-programmed cell death (PD)-1 monoclonal antibody that augments anti-tumour immune responses, has demonstrated benefit within the metastatic melanoma setting, with data from the CheckMate 067 trial showing significant OS benefit for nivolumab compared to ipilimumab that increases

over time [16]. Based on promising phase III trial results [17,18], nivolumab is now indicated for the adjuvant treatment of adults with melanoma with lymph node involvement or metastatic disease who have undergone complete resection [19,20].

This study describes analyses estimating comparative efficacy, safety and the impact on health-related quality of life (HRQoL) for nivolumab relative to routine surveillance in patients with stage III–IV melanoma. We undertook this study because no direct-head-to-head study exists assessing nivolumab versus routine surveillance and, as such, well-recognised statistical methods were used to estimate this comparison indirectly.

## 2. Methods

Patient-level data (PLD) were available for two key trials: CheckMate 238 (238; NCT02388906) and EORTC 18071 (18071; NCT00636168).

The 238 study is a phase III, randomised, double-blind trial in which patients with a high risk of recurrence after complete resection of stage IIIB/C or IV melanoma were randomised to nivolumab or ipilimumab (1:1 randomisation ratio) [17,18]. Randomisation was stratified by programmed cell death ligand-1 status (positive [based on 5% cut-off] versus negative/indeterminate) and AJCC disease stage (2009 classification—7th edition; stage IIIB/C versus stage IV M1a–M1b versus stage IV M1c). The primary outcome was RFS, and secondary outcomes include OS, DMFS, adverse events (AEs) and HRQoL (based on EQ-5D® and European Organisation for Research and Treatment of Cancer quality of life questionnaire [EORTC QLQ-C30] scores). The study was initiated in March 2015 with a primary completion date of 26th November 2018.

The 18071 study is a multi-national, randomised, phase III, double-blind trial in which patients were randomised to ipilimumab or placebo (1:1 randomisation ratio) after complete resection of high-risk stage III melanoma [12,21]. Randomisation was stratified by AJCC disease stage (2002 classification, 6th edition) and by region (North America, European countries and Australia). The primary outcome measure was RFS and key secondary outcomes included OS, DMFS, AEs and HRQoL (as assessed by EORTC QLQ-C30 scores). The study was initiated in June 2008 with a primary completion date of July 2013 and a study completion

date of November 2018. The placebo group within this trial serves to inform data on ‘routine surveillance’ for the purposes of this research.

### 2.1. Indirect treatment comparisons

An indirect treatment comparison (ITC) of nivolumab versus placebo (proxy for routine surveillance) can be formed using ipilimumab from both trials as a common comparator; the network of evidence is presented in Fig. 1.

Several analytical approaches were used to form the ITCs, and Bucher ITCs were performed as the primary analyses [22]. Bucher ITCs were chosen as they use aggregate results from two separate randomised controlled trials (RCTs; 238 and 18071) to compare two treatments (nivolumab and placebo) through a common comparator (in this case ipilimumab) while maintaining randomisation. This approach used Cox proportional hazards models to estimate relative treatment effect estimates (versus ipilimumab) within each study; these estimates were then used to derive the ITC relative treatment effect for nivolumab versus placebo. ITCs require an assumption of ‘similarity of trials’, that is, that studies in the network are comparable in terms of study design, patient population and distribution of treatment effect modifiers [23]. As such, differences in study population and design were explored before performing the ITCs.

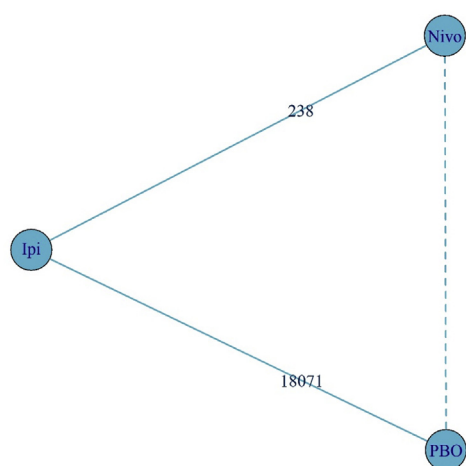
There are differences between the studies with respect to patient demographics (Table 1) and study design. The 238 study did not include patients with stage IIIA disease, whereas the 18071 study did not include patients with stage IV disease. It should also be noted that the 18071 study defined disease stage by AJCC, 6th edition,

whereas the 238 study used the 7th edition. This is unlikely to affect the ITC as the main difference between the 6th and 7th editions lies in the definition of stage IIIA disease, and 238 did not include patients with that stage of melanoma [7]. In addition, the 18071 study consisted entirely of patients with cutaneous melanoma, whereas in the 238 study, 88% had cutaneous melanoma (including ~3.5% with acral melanoma) and approximately 12% of patients had extracutaneous melanoma.

In addition to differences in patient characteristics, some study design/protocol differences existed between trials. These included differences in HRQoL data collection time points and treatment with ipilimumab. Protocol differences regarding treatment with ipilimumab is presented in Table 2. In 18071, treatment was permitted for up to a maximum of 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal, whereas in 238 treatment was permitted for only 1 year. Despite this difference in trial design, the median duration of ipilimumab was shorter in 18071, the patients in the ipilimumab arms for both trials received the same median doses, and only 25% of patients assigned to receive ipilimumab in 18071 received ipilimumab beyond 1 year.

Overall, patient characteristics were well balanced within studies and the patient characteristics were similar between the studies. However, a difference in the design of the studies with respect to stage of the included patients meant no overlap between trials for stage IIIA and IV patients. Aside from this there is also a larger proportion of stage IIIB patients in the 18071 study. Previously reported results for these studies have indicated that the relative treatment effect of RFS within studies is consistent between disease stages [12,17]; therefore, further statistical adjustment was not performed in our primary analyses. The primary analysis was performed for the intention-to-treat (ITT) population and assumed that the inclusion of stage IV patients in 238 and stage IIIA patients in 18071 did not impact the indirect treatment effect estimate between nivolumab and placebo. Given that PLD, and therefore subgroup data, were available for both studies, a sensitivity analysis was performed for the population of patients with stage IIIB/C disease.

Two further sensitivity analyses were performed (described further in the supplementary appendices) and assessed the robustness of the primary analysis using methods only available using PLD; the results of these analyses are provided in the supplementary appendices. In the first sensitivity analysis, within-study relative treatment effects were covariate-adjusted for factors known to be prognostic for outcomes; disease stage, age, sex and Eastern Cooperative Oncology Group (ECOG) performance status. The covariate-adjusted relative treatment effects were then used in the Bucher comparison. This sensitivity analysis controlled for differences between treatment arms within each study. In the



**Key:** Ipi, ipilimumab; Nivo, nivolumab; PBO, placebo.

**Notes:** solid line indicates direct evidence; dashed line indicates indirect evidence.

Fig. 1. **Network of evidence.** The solid line indicates direct evidence and the dashed line indicates indirect evidence. Ipi, ipilimumab; Nivo, nivolumab; PBO, placebo.

Table 1  
Summary of patient characteristics.

Characteristic	238		18071	
	Nivo (n = 453)	Ipi (n = 453)	Ipi (n = 475)	PBO (n = 476)
<b>Gender</b>				
Male (%)	258 (57.0)	269 (59.4)	296 (62.3)	293 (61.6)
<b>Age</b>				
Median (range)	56 (19–83)	54 (18–86)	51 (20–84)	52 (18–78)
<65 years old (%)	333 (73.5)	339 (74.8)	394 (82.9)	389 (81.7)
<b>Disease stage<sup>a</sup></b>				
IIIA (%)	0 (0.0)	0 (0.0)	98 (20.6)	88 (18.5)
IIIB (%)	163 (36.0)	148 (32.7)	213 (44.8)	207 (43.5)
IIIC (%)	204 (45.0)	218 (48.1)	164 (34.5)	180 (38.0)
IV (%)	82 (18.1)	87 (19.2)	0 (0.0)	0 (0.0)
Other/NR (%)	4 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)
<b>Disease stage<sup>a</sup> (IIIB/C subgroup)</b>				
IIIB (%)	163/367 (44.4)	148/366 (40.4)	213/377 (56.5)	207/387 (53.5)
IIIC (%)	204/367 (55.6)	218/366 (59.6)	164/377 (59.6)	180/387 (46.5)
<b>Stage III lymph node involvement</b>				
Microscopic (%)	125/369 (33.9)	134/366 (36.6)	210/475 (44.2)	193/476 (40.5)
Macroscopic (%)	219/369 (59.3)	214/366 (58.5)	265/475 (55.8)	283/476 (59.5)
NR (%)	25/369 (6.8)	18/366 (4.9)	0/475 (0.0)	0/476 (0.0)
<b>Stage III tumour ulceration</b>				
Present (%)	153/369 (41.5)	135/366 (36.9)	197/475 (41.5)	203/476 (42.6)
Absent (%)	201/369 (54.5)	216/366 (59.0)	257/475 (54.1)	244/476 (51.3)
NR (%)	15/369 (4.1)	15/366 (4.1)	21/475 (4.4)	29/476 (6.1)
<b>Melanoma subtype</b>				
Cutaneous (%)	404 (89.2)	395 (87.2)	475 (100.0)	476 (100.0)
Acral (%)	16 (3.5)	17 (3.8)	0 (0.0)	0 (0.0)
Extracutaneous (%)	49 (10.8)	58 (12.8)	0 (0.0)	0 (0.0)
Mucosal (%)	16 (3.5)	13 (2.9)	0 (0.0)	0 (0.0)
Other (%)	33 (7.3)	45 (9.9)	0 (0.0)	0 (0.0)
<b>ECOG PS</b>				
0 (%)	413 (91.2)	405 (89.4)	445 (93.7)	448 (94.1)
1 (%)	40 (8.8)	48 (10.6)	29 (6.1)	28 (5.9)
2 (%)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)

ECOG PS, Eastern Cooperative Oncology Group performance status; Ipi, ipilimumab; Nivo, nivolumab; n, number of patients; NR, not reported; PBO, placebo.

<sup>a</sup> 18071 defined disease stage using the American Joint Committee on Cancer, 6th edition, whereas 238 uses the 7th edition.

second sensitivity analysis, a pooled Cox model was used in which a single Cox regression model was fitted using PLD from both studies, including fixed-effect covariates for treatment and study.

For all analyses of 18071 data, the 13th May 2016 (approximately 60-month) data cut was used; note this was the data cut available at the time of the analysis.

For 238, the 28th January 2019 (36-month) data cut was used for RFS and DMFS. All HRQoL data were collected within 18 months of follow-up; as such HRQoL analyses were based on the 12th June 2017 (18-

month) data cut. All patients had been off randomised treatment for at least 100 days before 12th June 2017, therefore the 18-month data cut was used for the safety analyses.

## 2.2. End-points

### 2.2.1. Efficacy

The two efficacy end-points of interest for which data were reported in both studies were RFS and DMFS; OS data from CM238 were not reported as they were too immature at the time of this analysis. RFS was defined as the time from randomisation to recurrence, new primary melanoma or death. DMFS was defined as the time from randomisation to distant metastasis or death. However, the definition of the efficacy end-points differed between the trials in two ways: the trials had different primary reviewers and different definitions of subsequent therapy. As 238 is the pivotal trial for nivolumab in adjuvant melanoma, the primary definition of RFS in 238 was chosen for all analyses. In 238, the primary definitions of both RFS and DMFS were investigator assessed, and patients were censored at receipt of subsequent therapy. Data for the corresponding definitions of RFS and DMFS were not available for 18071 at the time of the analysis; the primary definitions in 18071 were independently assessed and did not censor patients at receipt of subsequent therapy. To match the primary definition in 238, the most similar available definitions of RFS and DMFS in 18071 were chosen for use in the ITC (i.e. patients were censored at receipt of subsequent therapy, but independent review had to be used).

### 2.2.2. Safety

The four safety end-points of interest for which data were reported in both studies were time to first: AE (any), serious AE, grade III–IV AE and AE leading to treatment discontinuation. Each safety end-point was defined as the time from randomisation to the specified event. The analysis of safety end-points only considered

Table 2  
Ipilimumab dosage and duration information.

238 study	18071 study
<ul style="list-style-type: none"> <li>• Ipilimumab 10 mg/kg every 3 weeks for four doses, then every 3 months up to a maximum of 1 year or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal.</li> <li>• Median duration = 2.7 months</li> <li>• Median number of doses = 4</li> </ul>	<ul style="list-style-type: none"> <li>• Ipilimumab 10 mg/kg every 3 weeks for four doses, then every 3 months up to a maximum of 3 years or until disease recurrence, unacceptable toxicity, major protocol violation or treatment refusal.</li> <li>• Median duration = 2.1 months</li> <li>• Median number of doses = 4</li> <li>• 25% of patients received ipilimumab beyond 1 year</li> </ul>



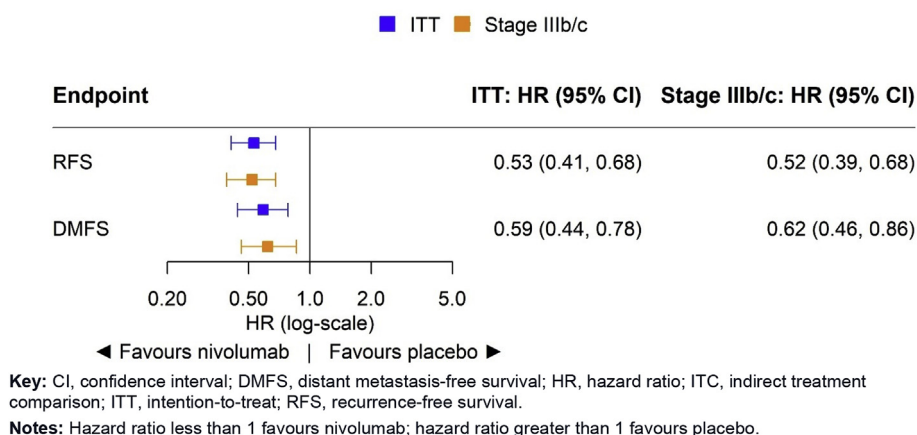


Fig. 2. **Bucher ITC efficacy results.** CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; RFS, recurrence-free survival.

treatment-emergent AEs. Patients who did not receive treatment were therefore excluded from the analysis (i.e. only the safety population was considered). For this analysis, treatment-emergent AEs were defined as AEs while on randomised treatment or within 100 days after treatment discontinuation in both 238 and 18071; note, the study definition considered in 18071 per protocol was 60 days. If a patient did not experience an event considered to be treatment emergent, they were censored 100 days after the end of randomised treatment or at the date patients were last known to be alive (if this was before 100 days after the patient discontinued treatment).

### 2.2.3. Health-related quality of life

To assess the HRQoL of patients treated with nivolumab in comparison to routine surveillance, time to deterioration for each QLQ-C30 domain was analysed. For each HRQoL end-point, time to deterioration was defined as the time from randomisation to the time where the specific score reduced by  $\geq 10$  compared to baseline; a score of 10 was chosen as 10% of the QLQ-C30 scale has previously been recommended as a clinically important change [24], and a change of 10 is the threshold most commonly reported by other studies [25]. Patients who did not deteriorate by a score of 10 were censored at the time of their last assessment, and patients without follow-up data were censored at baseline. For the analysis of each HRQoL end-point, patients' baseline values were included as a covariate. Patients who did not have a baseline record were excluded from the analysis along with patients who did not have any records at all. As a sensitivity analysis (described further in the [supplementary appendices](#)), the deterioration event was only considered an event when confirmed (i.e. deterioration of at least 10) by the following HRQoL record (or it was the final record).

## 3. Results

Results from the unadjusted Bucher ITC analyses in the overall ITT population are presented below. For the efficacy end-points (RFS and DMFS; [Fig. 2](#)), the results favour nivolumab over routine surveillance and are statistically significant at a 95% CI. The Bucher forest plot indicates that nivolumab significantly reduced the hazard of RFS events for both the ITT and overlapping stage IIIB/C populations (hazard ratio [HR]<sub>ITT</sub>: 0.53 [95% CI: 0.41, 0.68], HR<sub>stage IIIB/C</sub>: 0.52 [95% CI: 0.39, 0.68]) and DMFS events (HR<sub>ITT</sub>: 0.59 [95% CI: 0.44, 0.78], HR<sub>stage IIIB/C</sub>: 0.62 [95% CI: 0.46, 0.86]) relative to routine surveillance. Alternative methodology was explored in the form of a pooled Cox analysis and separately using covariate adjustment within the Bucher analysis. The findings of these analyses, presented in [Fig. 3](#), were consistent with the primary analyses.

Results of the safety end-point analyses ([Fig. 4](#)) show that the hazard of experiencing an AE (any AE) was significantly increased for patients who received nivolumab in comparison to those who received placebo for both the ITT and stage IIIB/C populations (HR<sub>ITT</sub>: 1.48 [95% CI: 1.22, 1.80], HR<sub>stage IIIB/C</sub>: 1.47 [95% CI: 1.19, 1.92]), as would be expected with an active treatment with known on target adverse effects. The results also indicate that patients receiving nivolumab had a significantly greater hazard of experiencing an AE leading to treatment discontinuation compared to patients receiving placebo for both the ITT and stage IIIB/C population (HR<sub>ITT</sub>: 2.03 [95% CI: 1.23, 3.33], HR<sub>stage IIIB/C</sub>: 1.77 [95% CI: 1.04, 3.02]). Similarly, there is a non-significant trend of patients experiencing an increased hazard of a serious AE while receiving nivolumab in comparison to placebo, whereas the hazard of experiencing a grade III–IV AE is similar between

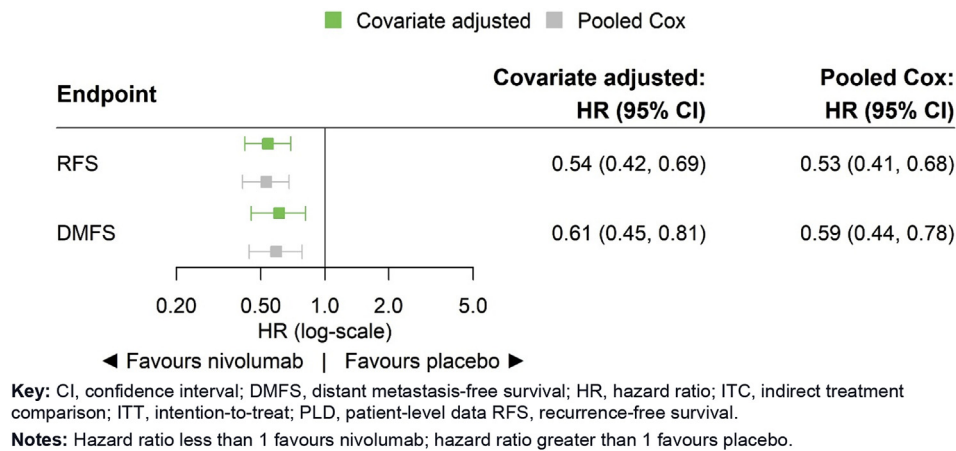


Fig. 3. ITC efficacy results—PLD sensitivity analyses. CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; PLD, patient-level data; RFS, recurrence-free survival.

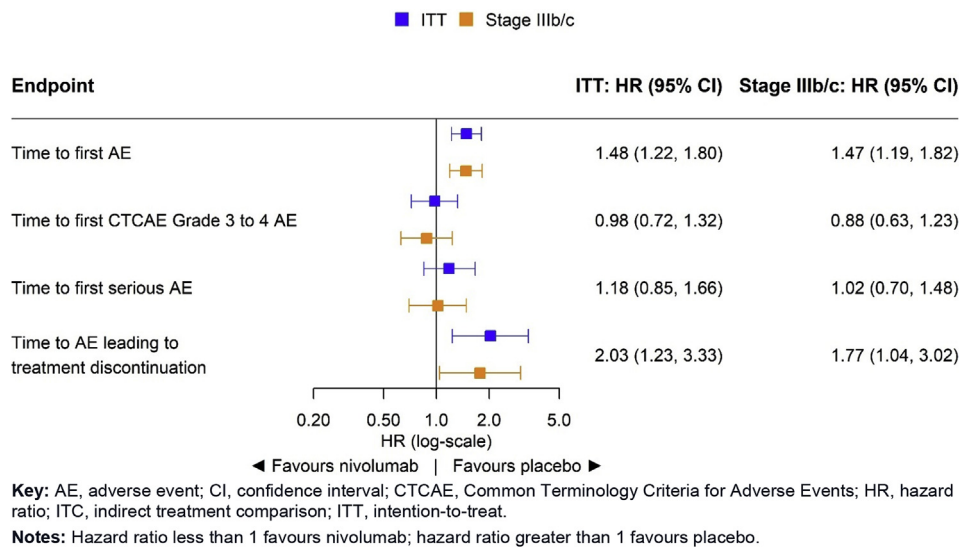


Fig. 4. Bucher ITC safety results. AE, adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat.

nivolumab and placebo. These findings were consistent with the covariate-adjusted analysis and the pooled Cox analysis presented in Fig. 5.

Results of the HRQoL comparisons (Fig. 6) show broadly similar results between nivolumab and placebo (HRs close to 1); 14 of the 15 comparisons were not statistically significant. The comparison of dyspnoea statistically favoured placebo over nivolumab for both the ITT and stage IIIB/C populations (HR<sub>ITT</sub>: 1.37 [95% CI: 1.01, 1.84], HR<sub>stage IIIB/C</sub>: 1.42 [95% CI: 1.01, 1.99]). These findings were consistent with the covariate-adjusted analysis and the pooled Cox analysis, presented in Fig. 7. The time to confirmed deterioration analysis (also presented in Fig. 7) yielded similar results; however, the dyspnoea analysis did not

significantly favour placebo, and there is a non-significant trend that nivolumab patients had a reduced hazard of experiencing a deterioration in pain or constipation.

Full ITC results for all end-points and primary and sensitivity analyses are presented in the [supplementary appendices](#).

#### 4. Discussion

Nivolumab has been shown to be a safe and efficacious treatment for patients after resection of melanoma with high risk of relapse [19,20]. Before nivolumab was approved in Europe, the standard of care was routine surveillance in many countries. This study explores how

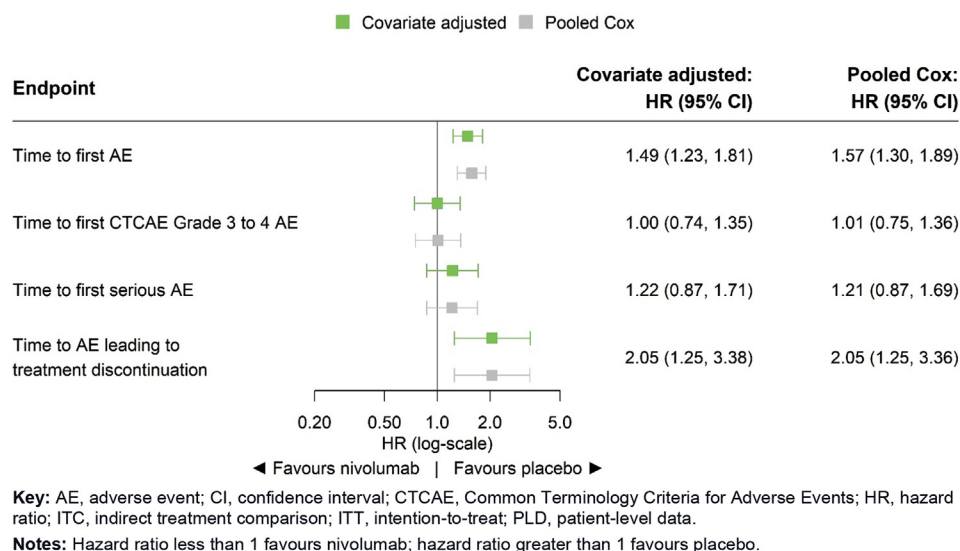


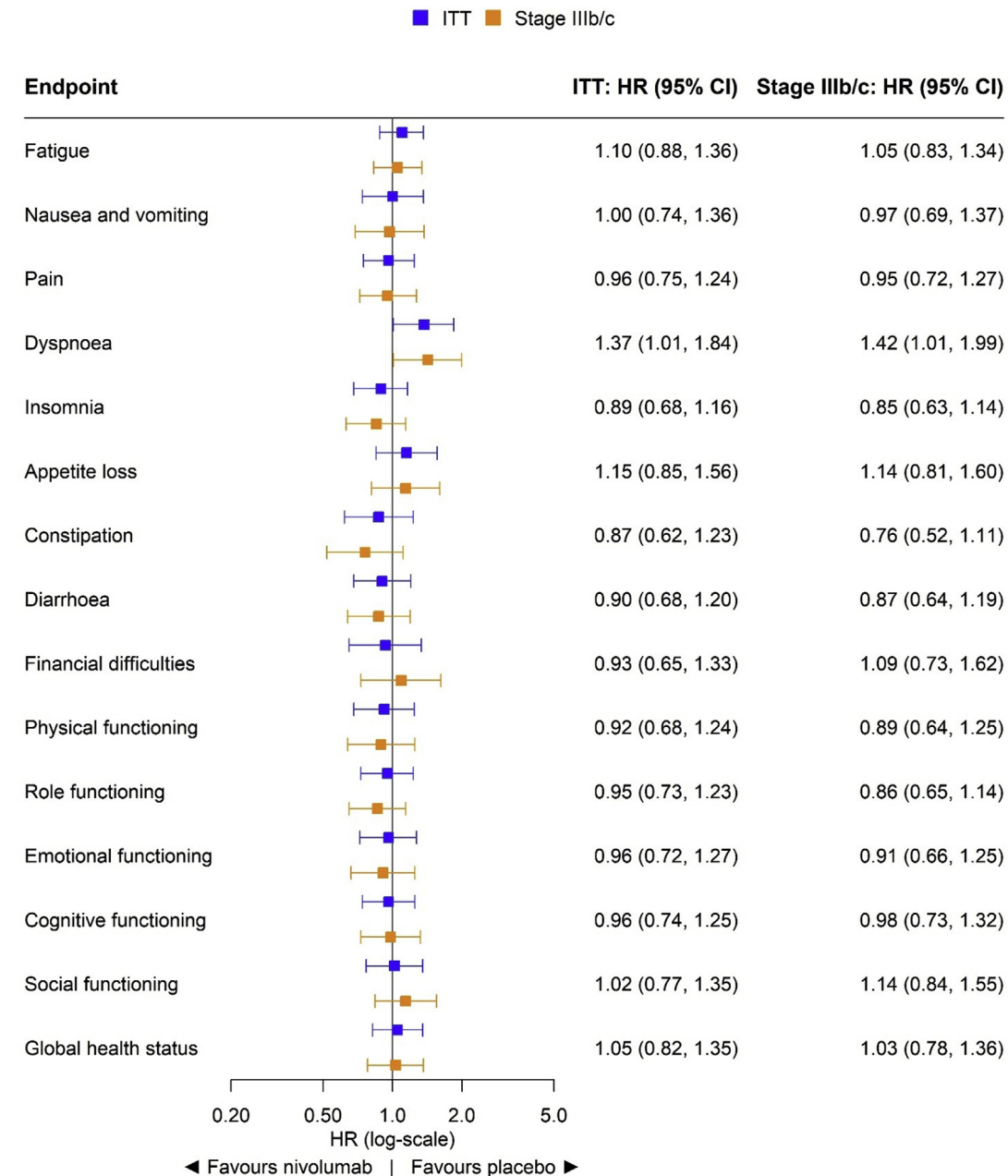
Fig. 5. ITC safety results—PLD sensitivity analyses. AE, adverse event; CI, confidence interval; CTCAE, Common Terminology Criteria for Adverse Events; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; PLD, patient-level data.

ITCs can estimate comparative efficacy, safety and HRQoL in the absence of head-to-head trials.

The results show that adjuvant treatment with nivolumab after resection provides a significant efficacy benefit over routine surveillance, whereas demonstrating a tolerable safety profile and similar HRQoL compared to routine surveillance. Consistent results were observed for each of the different end-points for the stage IIIB/C population, suggesting that the inclusion of the stage IIIA patients in 18071 and stage IV patients in 238 had minimal impact on the relative treatment effect.

To further explore the robustness of the ITC, alternative methodology was explored in the form of a pooled Cox analysis (to use all PLD rather than aggregate data), and separately Bucher analyses using relative treatment effects estimated following within trial adjustments for prognostic factors (to control for patient differences between treatment arms within each trial). The sensitivity analysis produced highly consistent results, suggesting that additional covariate adjustment had minimal impact on results providing confidence that the analysis method does not unduly influence the results. The ability to explore multiple analytical approaches using standard ITC methods and adjustments using PLD approaches is a key strength of this research. In addition, the evidence network used within these ITCs is very small (two trials); therefore, issues regarding heterogeneity between trials are limited relative to complex networks of evidence with many contributing RCTs. The observed heterogeneity between the two trials was explored analytically where possible using PLD; most notably, the difference between trials such as differences in the disease stage of patients, and this did not affect the ITC findings.

As with any ITC analyses, there are some limitations to consider when interpreting the results. In addition to unmeasured trial-specific confounders, heterogeneity between the two trials included independent versus investigator assessment for RFS, ipilimumab treatment duration, disease stage definitions, and differences in inclusion criteria. Implicitly, the ITCs assume that these factors do not affect the within trial relative treatment effect estimates. It is not known that these assumptions bias the ITC results in one direction or the other. For the analysis of safety end-points, the results compared the rate at which patients first experienced a particular AE; however, this does not provide any information about the number of future events or AE duration, limiting the indirect comparison of safety end-points in this analysis. It should be noted that the publication of safety data for nivolumab in the 238 study is consistent with the known safety profile of nivolumab reported across other tumours [18,26]. Given the clinically meaningful benefit of nivolumab therapy, the risk benefit assessment of treating in the adjuvant setting is considered favourable [26]. For the analysis of HRQoL, the well-established cut-off of a 10-point decrement was chosen as the minimum important difference [24,25]. Further analyses using different minimum important differences per QLQ-C30 domain and changes in HRQoL over time were not assessed [27]. It has been suggested that HRQoL deterioration of patients with adjuvant melanoma is driven by disease recurrence more than the toxicity of the treatment received [15]. It is also important to acknowledge that standard cancer HRQoL instruments used in these studies may not be specific and sensitive enough to detect treatment-related QoL impacts of immuno-oncology therapies. Such limitations,



**Key:** CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HRQoL, health-related quality of life.

**Notes:** Hazard ratio less than 1 favours nivolumab; hazard ratio greater than 1 favours placebo; each endpoint is time to deterioration in each QLQ-C30 domain.

Fig. 6. **Bucher ITC HRQoL results.** Each end-point is time to deterioration in each QLQ-C30 domain. CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; HRQoL, health-related quality of life.

including differences in how HRQoL data were collected in both studies, should be considered when interpreting the results.

It is important to note that additional active treatments in this indication are also now available and under development, meaning that a larger network of evidence for treatments for adjuvant melanoma exists. A network meta-analysis comparing available treatment options have been explored [28].

In conclusion, the ITCs performed showed a significant advantage of nivolumab over placebo for the efficacy outcomes RFS and DMFS, whereas producing results which suggested patient's overall HRQoL were not compromised. Furthermore, the 238 study demonstrates continued RFS benefit for nivolumab relative to an active comparator, ipilimumab, with median RFS not reached after 3 years follow-up. As such nivolumab is an important addition to the treatment options for



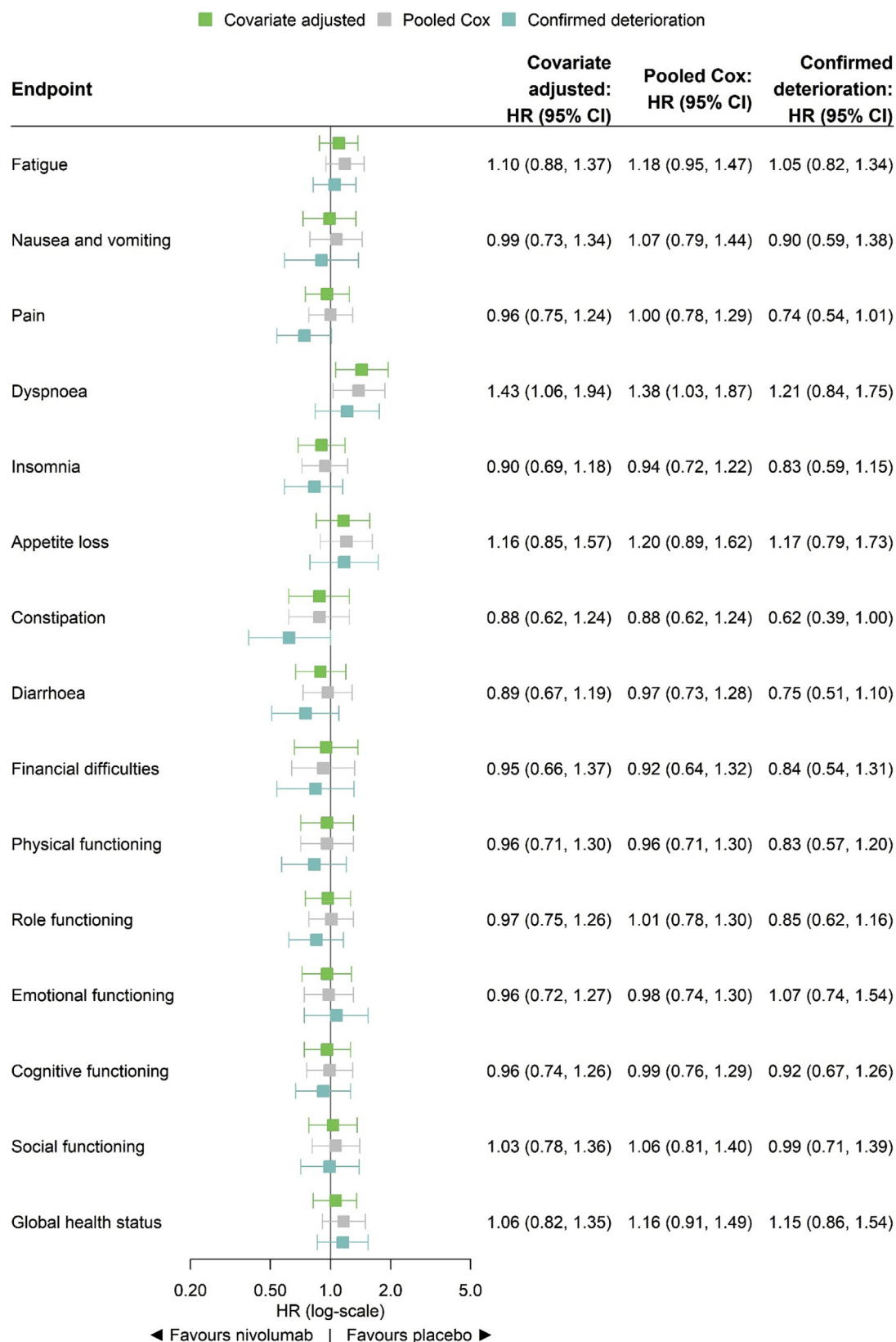


Fig. 7. ITC HRQoL results—PLD sensitivity analyses. Each end-point is time to deterioration in each QLQ-C30 domain. CI, confidence interval; HR, hazard ratio; ITC, indirect treatment comparison; ITT, intention-to-treat; PLD, patient-level data; HRQoL, health-related quality of life.

this disease, addressing the unmet medical need for patients at high risk of recurrence.

### Conflict of interest statement

M.H. and N.R. are employees of BresMed Health Solutions; BresMed Health Solutions were paid consultants on this research. A.A., K.K., K.G. and S.K. are employees and shareholders of Bristol-Myers Squibb. D.S. and M.R.M. reported no conflicts of interest in relation to this publication and has received personal fees and/or grants and, non-financial support (such as research funding, honoraria travel and accommodation) from Bristol-Myers Squibb and other pharmaceutical companies including but not limited to Novartis, MSD and Roche.

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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.2020.03.011>.

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