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Adjuvant pembrolizumab versus interferon alfa-2b or ipilimumab in resected high-risk melanoma

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Abstract

We conducted a randomized phase 3 trial to evaluate whether adjuvant pembrolizumab for one year (648 patients) improved recurrence-free survival (RFS) or overall survival (OS) in comparison to high-dose interferon alfa-2b for one year or ipilimumab for up to three years (655 patients), the approved standard-of-care adjuvant immunotherapies at the time of enrollment for patients with high-risk resected melanoma. At a median follow-up of 47.5 months, pembrolizumab was associated with significantly longer RFS than prior standard-of-care adjuvant immunotherapies (hazard ratio [HR] 0.77; 99.62% confidence interval [CI] 0.59–0.99; P=0.002). There was no statistically significant association with OS among all patients (HR, 0.82; 96.3% CI 0.61–1.09; P=0.15). Proportions of treatment-related adverse events of grades 3 to 5 were 19.5% with pembrolizumab, 71.2% with interferon alfa-2b, and 49.2% with ipilimumab. Therefore, adjuvant pembrolizumab significantly improved RFS but not OS compared to the prior standard-of-care immunotherapies for patients with high-risk resected melanoma.

Introduction

Several therapies have demonstrated an improvement in OS when used as initial treatment for patients with unresectable metastatic melanoma, including ipilimumab (1) and nivolumab alone or in combination (2), pembrolizumab (3), and combinations of BRAF and MEK inhibitors (4–7). In recent years, several of these approaches have been utilized in the adjuvant setting to prevent recurrence of melanoma after surgical excision (8). Adjuvant immunotherapy with high-dose interferon alfa-2b, ipilimumab (cytotoxic T lymphocyte antigen 4 [CTLA-4] blocking antibody, administered at 10 mg per kilogram of body weight every three weeks), or with nivolumab or pembrolizumab (programmed cell death 1 [PD-1] blocking antibodies), improved RFS in randomized clinical trials enrolling patients with completely resected melanoma at high risk of recurrence (9–13); and all are approved for adjuvant use in melanoma by the United States Food and Drug Administration (FDA). High-dose interferon alfa-2b and ipilimumab have each been shown to improve OS compared to an observation or placebo control group in randomized adjuvant therapy trials (9,10). These adjuvant immunotherapy trials enrolled patients with different but partially overlapping stages of melanoma. The European Organization for Research and Treatment of Cancer (EORTC) 1325 (KEYNOTE-054) clinical trial involved a high-risk patient population with stage III melanoma, and demonstrated a 43% lower recurrence or death in patients receiving adjuvant pembrolizumab compared to placebo (12,13). CheckMate 238 enrolled patients

with resected higher-risk stage III and stage IV metastatic melanoma; nivolumab showed a 35% improvement in RFS compared to ipilimumab (11). The combination of nivolumab and ipilimumab (the latter given at 1 mg per kilogram every six weeks) was tested in a similar population and did not improve RFS over adjuvant nivolumab (14). It is currently unknown if the use of adjuvant anti-PD-1 therapy improves OS in patients with high-risk resected melanoma. In parallel to the testing of adjuvant immunotherapies for melanoma, adjuvant therapy with the BRAF inhibitor dabrafenib together with the MEK inhibitor trametinib for patients with resected stage III melanoma with a *BRAF* V600E/K mutation demonstrated an improvement in RFS and distant metastasis-free survival compared to placebo(15). In this trial, OS was reported with the first interim analysis, but the protocol prespecified number of events had not been reached by year 5 (15).

We conducted a randomized phase 3 clinical trial in patients with completely resected melanoma at high risk of recurrence comparing adjuvant pembrolizumab with either of the two standard-of-care adjuvant immunotherapies at the time, which had previously been shown to improve OS over observation or placebo: the high-dose interferon alfa-2b regimen (9) and ipilimumab at 10 mg per kilogram of body weight every three weeks (10). RFS and OS were both primary endpoints in order to determine if adjuvant pembrolizumab therapy would change the course of disease permanently, or if active therapies at the time of recurrence could attenuate differences between patients receiving adjuvant pembrolizumab or the prior standard-of-care adjuvant immunotherapies.

Results

Patients and Trial Regimen

A total of 1,301 eligible patients were randomized from 211 sites in the United States, Canada and Ireland: 647 patients were assigned to the pembrolizumab group, and 654 to the standard-of-care group (Fig. 1). The characteristics of the patients at randomization were similar in the two groups (Table 1). When the trial first opened, standard-of-care adjuvant therapy consisted of high-dose interferon alfa-2b (9). After the FDA approval of adjuvant ipilimumab (10), the protocol was amended to add ipilimumab as a treatment choice. Before the protocol amendment in April 2016, 74 patients had been randomized: 35 to interferon alfa-2b and 40 to pembrolizumab. Among all eligible patients, 8 randomized to pembrolizumab and 89 randomized to standard-of-care did not receive the assigned regimen. Among the patients in the standard-of-care group who received the assigned treatment, 420 received ipilimumab and 145 received interferon alfa-2b (Fig. 1).

Of the 639 patients who received pembrolizumab, 108 (16.9%) discontinued the regimen due to an adverse event. Among the 565 patients who received standard-of-care therapy, 308 (54.4%) discontinued the regimen due to an adverse event. A total of 134 (21.0%) in the pembrolizumab group discontinued the regimen because of disease recurrence, as compared to 92 (16.3%) in the standard-of-care group. A total of 365 patients (57.1%) in the pembrolizumab group and 50 (8.8%) in the standard-of-care group completed the regimen as stipulated in the protocol (Fig. 1). The median duration of follow-up for the patients alive was 47.0 months among patients randomized to pembrolizumab and 45.7 months randomized to standard of care.

Efficacy

Primary Endpoints—The protocol established that the final analysis for RFS and OS would occur after the planned number of events had happened, or at 3.5 years after the last patient was randomized if the anticipated number of events had not yet been reached. As 3.5 years had passed without reaching the planned number of events, the clinical trial was analyzed for the primary endpoints, at which point 98% of the anticipated RFS events and 57% of the anticipated OS events had occurred. In the intent-to-treat population, RFS was significantly longer in the pembrolizumab group than in the standard-of-care group; HR for recurrence or death 0.77 (99.62% CI, 0.59 to 0.99; log-rank P=0.002) (Fig. 2A). The RFS was also longer favoring pembrolizumab in the subgroup of patients with PD-L1 positive melanoma, with a HR of 0.69 (95% CI, 0.58 to 0.84) (Supplementary Fig. 1A). In the intent-to-treat population, the HR for OS was 0.82 (pembrolizumab:standard-of-care) with 96.3% CI, 0.61 to 1.09; log-rank P=0.15 (Fig. 2B). In the subgroup of patients with PD-L1 positive melanoma, the HR for OS was 0.84 with 97.8% CI, 0.59 to 1.22; log-rank P=0.29 (Supplementary Fig. 1B).

Post-recurrence Outcomes—We performed an exploratory analysis of post-recurrence OS, which was not significantly different between the two arms; HR for death 1.20, (95% CI, 0.90, 1.61). PD-1 blocking antibodies as a single drug were the most commonly used regimen after recurrence in the standard-of-care group (39% of patients); 14% of patients in the pembrolizumab group received single-agent PD-1 antibody therapy (Supplementary Table 1). Other post-recurrence therapies included anti-PD-1 in combination with anti-CTLA-4 or other immune-modulating agents, anti-CTLA-4 alone, intralesional oncolytic therapy, interleukin-2, interferon alfa-2b, BRAF and MEK inhibitor targeted therapies, radiation and surgery. Thirty percent of the patients in both groups did not have data available regarding post-recurrence treatment. The predominant site of first recurrence was distant (60% with pembrolizumab, 71% with standard-of-care). Proportions of local, in-transit, and regional recurrences in the pembrolizumab group were 16%, 12%, and 11%, respectively; proportions in the standard-of-care group were 9%, 8%, and 13%, respectively (Supplementary Table 1).

RFS and OS According to Other Variables—The between-group associations in RFS observed in the overall population were consistently observed across subgroups based on baseline characteristics, including according to sex, age, standard-of-care therapy received, and stage of disease, with the possible exception that the group with macroscopic lymph node involvement may derive more improvement from pembrolizumab compared to microscopic lymph node involvement (Fig. 3; RFS macroscopic/microscopic interaction $P = 0.08$, all other interaction $P > 0.22$). Patients with PD-L1 positive tumors in the standard-of-care group may derive improvement in post-progression OS compared to the pembrolizumab group (Supplementary Fig. 2; interaction $P = 0.09$). Otherwise, between-group associations for overall population OS and post-recurrence OS were similar across subgroups (overall population OS: Supplementary Fig. 3, all interaction $P > 0.28$; post-recurrence OS: Supplementary Fig. 2, all other interaction $P > 0.54$).

Among the 97 patients who did not receive therapy as assigned by the study randomization, 52 (54%) withdrew consent for further follow-up or were lost to follow-up within 30 days of randomization, and RFS and OS were censored at this time. There was no evidence of a difference in RFS or OS comparing patients who received therapy per protocol (n=1204) versus the patients who did not (n=97); HR for recurrence or death (not treated:treated) 1.44 with 95% CI, 0.89 to 2.13 and HR for OS 1.41 with 96.3% CI, 0.66 to 3.02. RFS and OS results in the subset of patients who received therapy per protocol (n=1204, safety population) were similar to results in the intent-to-treat population (n=1301); HR for recurrence or death 0.75 with 99.62% CI, 0.58 to 0.97 and HR for OS 0.78 with 96.3% CI, 0.58 to 1.04. In a final exploratory analysis, we analyzed the RFS data according to the two treatment options in the standard-of-care group, high dose interferon or ipilimumab (Supplementary Fig. 4). In a Cox regression model for RFS comparing the interaction between randomized group with pre-randomization standard-of-care choice is P = 0.49, indicating no strong evidence of heterogeneity in treatment arm association with RFS by pre-randomization standard-of-care treatment choice.

Safety—Adverse events of any grade related to the trial regimen occurred in over 90% of patients: in 583 patients (91%) treated with pembrolizumab, 401 (95%) treated with ipilimumab, and 143 (99%) treated with interferon alfa-2b (Table 2). Proportions of grade 3 and higher adverse events related to treatment were 17%, 43%, and 66% among patients treated with pembrolizumab, ipilimumab, and interferon alfa-2b respectively. Fatigue (59%) and maculo-papular rash (29%) were the most common events among patients treated with pembrolizumab, while fatigue (51%) and diarrhea (48%) were most common among patients treated with ipilimumab; and fatigue (88%) and aspartate aminotransferase increase (70%) were most common among patients treated with interferon alfa-2b (Table 2). Pneumonitis was an uncommon event in all of the treatment arms, and since its frequency was less than 10%, it is not included in Table 2. Among patients treated pembrolizumab pneumonitis of any grade was observed in 4.1 % of patients, and grade 3 pneumonitis in 0.6%. Among patients treated with ipilimumab, the proportions of pneumonitis were 5.0% (all grades) and 1.4% (grade 3), and among patients treated with interferon alfa-2b, they were 2.0% (all grades) and 0% (grade 3). Supplementary Table 2 provides information on any-causality adverse events in 10% or more of patients with any of the three treatment regimens. There was one death due to myocarditis in the pembrolizumab group attributed by the investigators to the treatment, and two among patients receiving ipilimumab, one due to colitis and one due to pneumonitis.

Discussion

In this randomized phase 3 trial comparing pembrolizumab to either ipilimumab or interferon alfa-2b for the treatment of patients with resected, high-risk stage III and stage IV melanoma, pembrolizumab was associated with a statistically significant 23% improvement in RFS. For OS, the HR of 0.82 was not statistically significant. A HR of 0.84 without statistical significance was also seen in the subgroup of patients with tumor PD-L1 expression. The RFS benefit observed in this trial is in the range of what has been shown with nivolumab compared to ipilimumab in a similar population of patients with resected

stage III or IV melanoma in the Checkmate-238 trial (11). The KEYNOTE-054 study compared pembrolizumab to placebo in patients with resected stage III cutaneous melanoma and also demonstrated an improvement in RFS (12,13). Therefore, three large adjuvant clinical trials have shown consistent improvement in RFS with the adjuvant administration of an anti-PD-1 therapy. The consequent question of whether adjuvant anti-PD-1 therapy improves OS, has not been reported as final results in the KEYNOTE-054 trial (12,13) and showed a non-significant 2% difference at 4-years in the Checkmate-238 trial, analyzed at 73% of the survival events needed for significance (16). In the current trial, pembrolizumab improved OS by 18%, which also did not meet the pre-specified level of significance when analyzed at 57% of the originally planned survival events. The difference in RFS and OS benefit in our trial may reflect the use of other widely available effective therapies for patients with melanoma recurrence (2–7), or may in part reflect the assessment of OS at a fixed time per protocol, leading to a smaller number of events than would have been necessary for a fully powered event-driven analysis. However, since OS is highly dependent on the availability of post-recurrence therapies, which tend to improve over time, it is unlikely that this result would change with later evaluations.

One of the study findings was that the first recurrence at distant sites was 11% higher in the standard-of-care treatment group. This was due to an apparent increase in local and in-transit recurrences in the pembrolizumab arm (12% higher), while both groups had a similar proportion of recurrence events in regional lymph nodes. These are exploratory findings and their significance is hard to determine with this dataset. We also note here that the early relapse rate at the first scan visit was very high in our study as has been observed in previous adjuvant therapy melanoma trials (11,13), and was consistent between both arms. This finding suggests that the ability to detect distant disease at baseline is limited using current imaging scans and physical exam alone. We are hopeful highly sensitive blood-based markers for minimal residual disease will improve our confirmation of baseline disease free status.

Efforts testing neoadjuvant therapy with immune checkpoint inhibitors in melanoma are currently underway. Multiple regimens have been tested in small feasibility studies including a single dose of pembrolizumab, varying strengths and doses of nivolumab plus ipilimumab, and monotherapy versus combination of immune checkpoint blockade (17–20). However, it is currently not known whether it is superior to give systemic therapy before or after surgery of resectable melanoma. A large, randomized trial powered to detect differences in event-free survival known as S1801 is currently enrolling in the US cooperative groups, and compares adjuvant pembrolizumab given as described in the current study versus 3 doses of neoadjuvant pembrolizumab followed by 15 doses of adjuvant pembrolizumab given every 3 weeks.

In conclusion, pembrolizumab as adjuvant therapy for patients with high-risk resected stage III and stage IV melanoma improves RFS in comparison to the prior standard-of-care adjuvant immunotherapies, but a similar association with OS was not observed among all patients or in the subset of patients with PD-L1 positive tumors. The safety profile of pembrolizumab is consistent with the toxicity spectrum that has been already defined for this

agent. Single-agent anti-PD1 antibody treatment should be considered the standard-of-care for adjuvant immunotherapy of high-risk melanoma.

Methods

Patients

The SWOG clinical trial S1404 enrolled patients from December 2015 to October 2017 who were 18 years of age or older with histologically confirmed cutaneous, acral or mucosal melanoma, and were within 98 days from definitive surgery. Patients had resectable stage IIIA (N2a), IIIB, IIIC, or IV disease defined by the American Joint Committee on Cancer 2009 classification, 7th edition (21). A complete regional lymphadenectomy was required for all patients with stage III disease. Imaging studies to document melanoma-free status at enrollment included either a total body positron emission tomography combined with computed tomography (CT) of diagnostic quality or a CT of the chest, abdomen and pelvis with contrast, and a magnetic resonance imaging or CT scan of the brain with intravenous contrast. Main exclusion criteria included prior immunotherapy in any setting for melanoma, active autoimmune disease that had required systemic treatment within two years of study entry, uveal melanoma, and a history of brain metastasis. For full information on eligibility criteria see the protocol in the Appendix. Tumor tissue was required for central pathological evaluation for PD-L1 expression by immunohistochemistry using the 22C3 antibody as previously described (22), and was scored on a scale of 0 to 5 (with higher numbers reflecting a higher level of PD-L1 expression); a score of 2 or higher (staining on greater than 1% of cells) was considered to indicate PD-L1 positivity. The clinical trial was registered as ClinicalTrials.gov number NCT02506153.

Trial Design and Regimen

This was an open-label randomized phase 3 study. Patients were randomized to receive either intravenous infusion of 200 mg of pembrolizumab every three weeks for a total of 18 doses, or an approved standard-of-care adjuvant immunotherapy. When the trial was first opened, the standard-of-care consisted of high-dose interferon alfa-2b, given intravenously at 20 million units per meter squared of body surface area per day, 5 days per week for four weeks followed by 10 million units per meter squared of body surface given subcutaneously three times per week for 11 months (9). After the FDA approval of adjuvant ipilimumab in October of 2015, the protocol was amended in April 2016 to add the choice of ipilimumab dosed at 10 mg per kilogram of body weight intravenously every three weeks for four doses followed by the same dose as maintenance every 12 weeks for up to 11 doses (10). Block randomization (1:1 ratio; block sizes varied: 6, 8, 10; sequence pre-specified by SWOG) was performed centrally using the National Cancer Institute (NCI) web-based OPEN platform and stratified according to stage, PD-L1 melanoma staining, and the planned standard-of-care regimen.

Assessments

Investigator-assessed recurrence was based on imaging or physical exam, with biopsy confirmation whenever possible. Clinical assessment and whole-body imaging occurred every 3 months for the first 2 years beyond randomization, and then every 6 months. Brain

imaging was performed annually. Beyond year 5, no study-specific imaging was required, but RFS and OS status were to be monitored up to 10 years. Adverse events were scored using NCI Common Terminology Criteria for Adverse Events, version 5.0.

Trial Oversight

The trial was sponsored by SWOG, the NCI, and Merck Sharp & Dohme Corp. The initial protocol and all amendments were reviewed and approved by SWOG, the NCI, the NCI Central Institutional Review Board, and at each institution. Each study subject provided voluntary, written, informed consent as approved by the human subject protection committee of each institution. The work was conducted in compliance with all ethical guidelines including good clinical practice standards and the Declaration of Helsinki. The data were collected by staff at each site and monitored by SWOG. The data were analyzed and interpreted by the authors. All authors had access to the full data used in the manuscript, and attest that the study as reported here follows the protocol.

Statistical Analysis

The three primary endpoints were: RFS, OS and OS in the subgroup with PD-L1-positive tumors. RFS was measured from date of randomization to date of first of recurrence or death from any cause; patients last known to be alive without recurrence were censored at date of last contact. OS was measured from date of randomization to date of death from any cause; patients last known to be alive were censored at the date of last contact. Models for power and sample size calculations are detailed in the protocol. Full information was 536 RFS and 374 OS events in the overall population. Per protocol, the final analysis would occur at 3.5 years after the last patient was randomized if the anticipated number of events had not yet been reached. Alpha allocation to control the study-wise error to under 0.05 is detailed in the Supplemental Materials. The alpha levels for these analyses are 0.0038 for RFS, 0.037 for OS in the overall population, and 0.023 for OS in the PD-L1 positive subgroup (the alpha in the PD-L1 positive subgroup accounts for the correlation between the subgroup and overall population, and maintains the study-wise alpha below 0.05 with calculations per Speissens and DuBois) (23). Baseline characteristics were compared between groups with Wilcoxon rank sum tests and Fisher’s exact tests. All three primary analyses were based on stratified log-rank tests in the intent-to-treat population. RFS and OS were estimated using the Kaplan-Meier method and Cox regression models were fit. A non-randomized comparison of survival from recurrence by randomized treatment was also performed. For primary endpoint analyses, confidence intervals are reported to match the alpha level of the test. For other analyses, 95% confidence intervals are reported. Two-sided p-values are reported. Toxicity was summarized among patients who received at least one dose of protocol therapy. All analyses were performed in R (version 4.0.2) and SAS (version 9.4).

Data availability—All data (to replicate every analysis in the manuscript and any Supplementary Information) will be posted to the NCI NCTN Data Archive per NCTN policy (https://nctn-data-archive.nci.nih.gov). Patient-level data, including a data dictionary, will be available within 6 months of publication through the United States NCTN/NCORP Data Sharing Archive (https://nctn-data-archive.nci.nih.gov) following the Data Sharing Archive policies. De-identified patient-level data, including the numbers, tables and figures

in the paper, will be made available. The protocol (including the statistical analysis plan in section 11 of the protocol) and the informed consent form are available in the Supplementary Information.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflicts of Interest

No potential conflicts of interest reported for R. Conry, P. Funchain, K. Gunturu, D. Johnson, K. Kendra, M. Kovacsovics-Bankowski, H. Li, J. Moon, E. Sharon, T. Truong.

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S. Ebbinghaus reports employment at Merck, and owns stock in Merck.

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Statement of significance

Adjuvant PD-1 blockade therapy decreases the rates of recurrence, but not survival, in patients with surgically resectable melanoma, substituting the prior standard-of-care immunotherapies for this cancer.

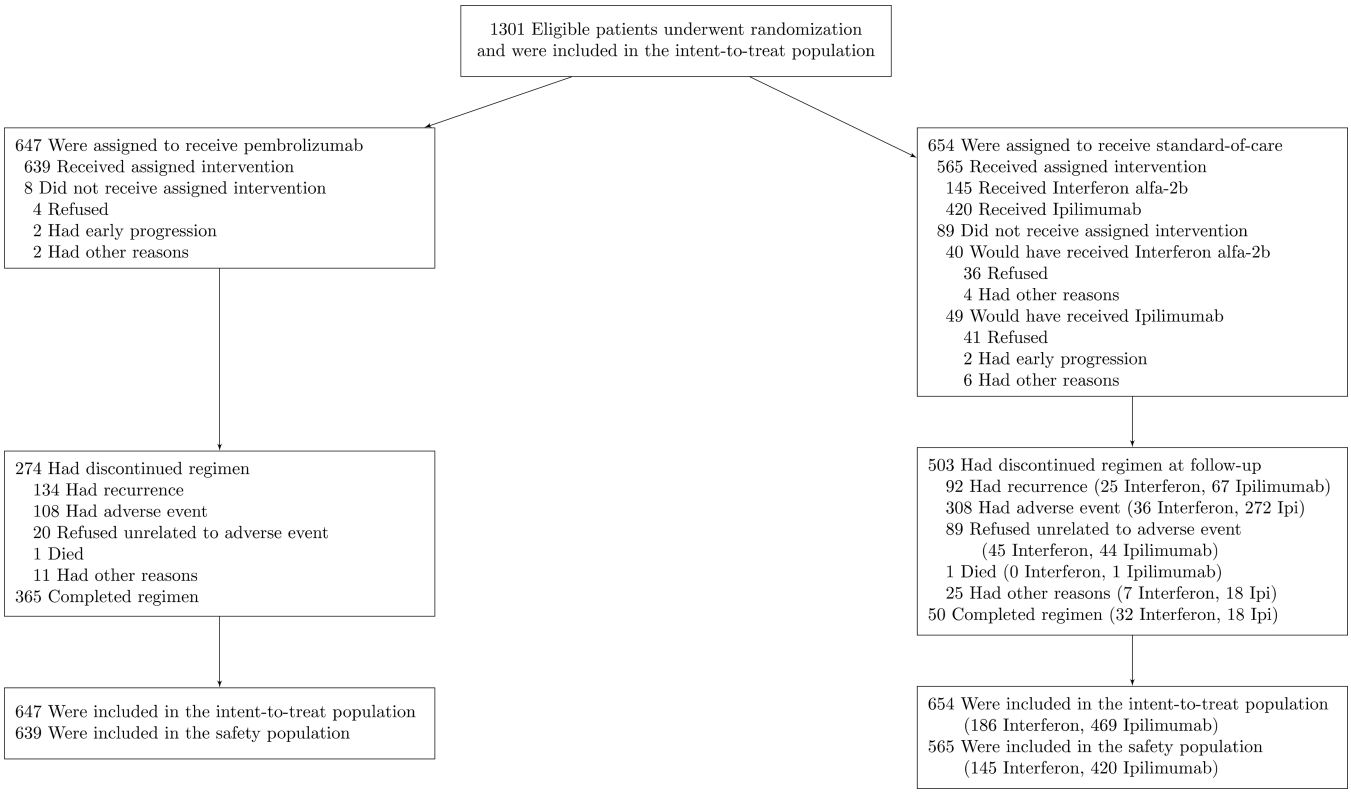

Figure 1. Enrollment, randomization, and follow-up.

All eligible patients who were randomized were included in the intention-to-treat population. The safety population included all patients who received at least one dose of treatment that they were randomly assigned. In total, 24 patients in the pembrolizumab group and 20 patients in the standard of care group were found to have major eligibility violations and were excluded from analyses.

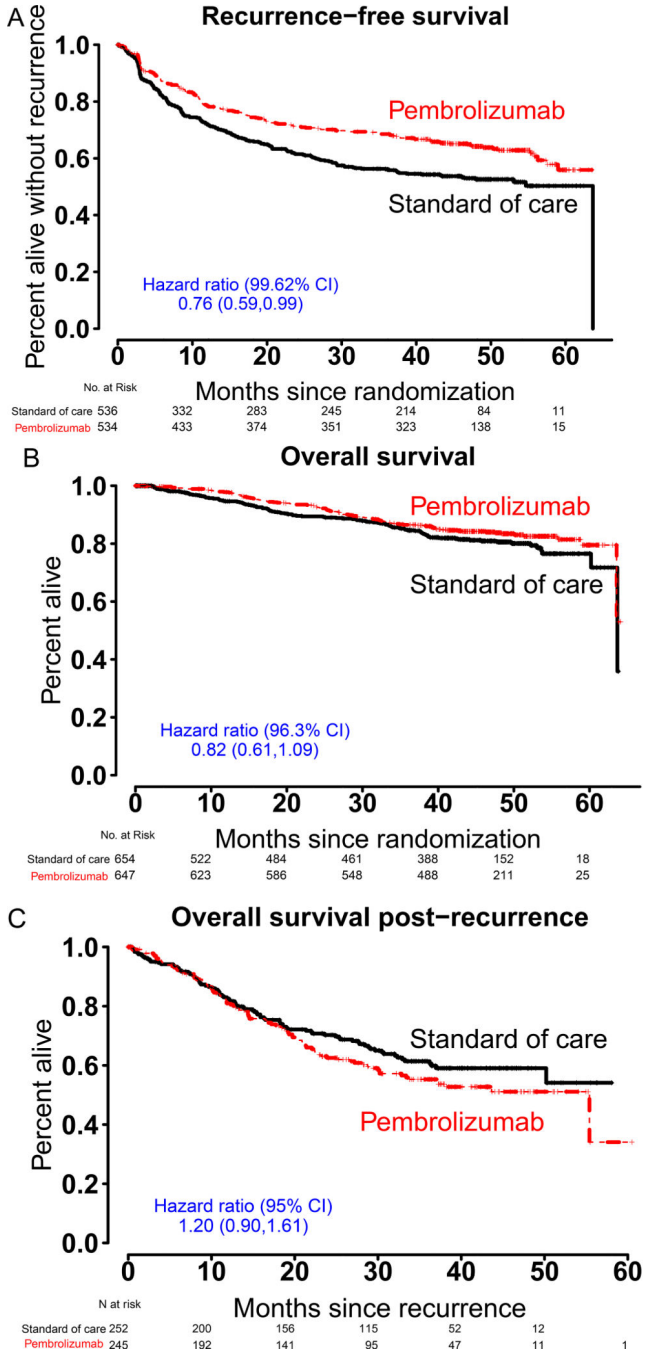

Figure 2. Kaplan-Meier estimates of main time-to event endpoints.

A) recurrence-free survival (as assessed by local investigators), B) OS in the intention-to-treat population, and C) exploratory analysis of post-recurrence OS. Cox regression models were stratified by randomization stratification factors: PD-L1 status, intended standard of care regimen choice, and stage of disease. Hazard ratios report pembrolizumab versus standard of care (reference). In the intention-to-treat analysis for RFS there were 524 events (252 in the pembrolizumab group, and 272 in the control group). The HR for recurrence was 0.77 (99.62% confidence interval [CI], 0.59 to 0.99). OS analysis was completed at

the protocol specified time of 3.5 years with 57% of events. There was not a statistically significant difference between the pembrolizumab group and the control group (0.82, 96.3% CI 0.61, 1.09). The post-recurrence analysis of OS was not a protocol-specified endpoint; it is included to provide information to evaluate post-recurrence outcomes in both study groups.

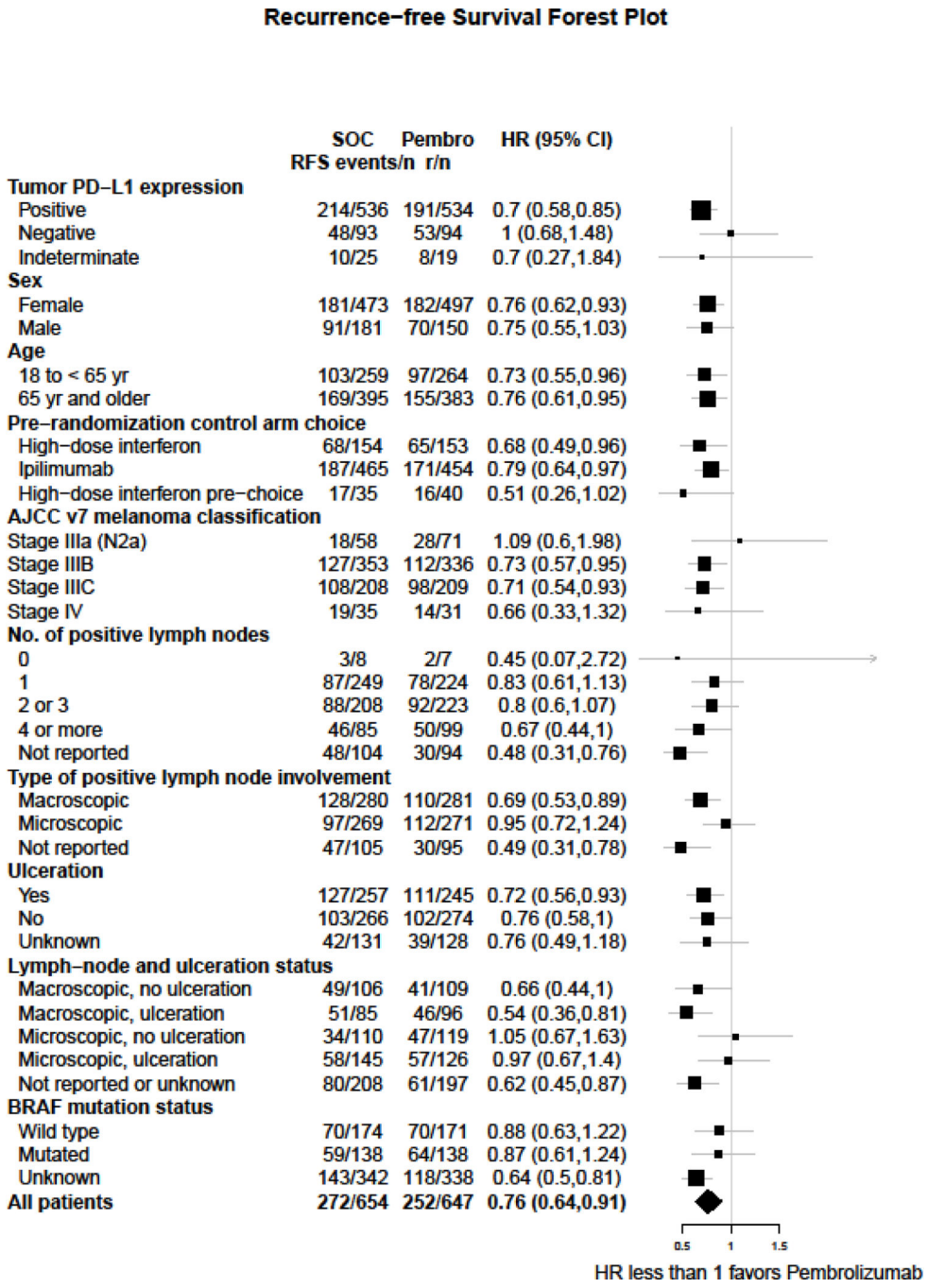

Figure 3. Forest plot for recurrence-free survival according to subgroup in the overall population.

An unstratified Cox regression model was used to estimate the hazard ratios of recurrence or death in the pembrolizumab group as compared to the standard of care group among all the patients. A stratified Cox regression model stratified by the randomization stratification factors (PD-L1 status, control arm choice, and stage of disease) is reported for the overall population. 95% confidence intervals are presented.

Table 1.

Demographic and Clinical Characteristic of Patients at Randomization.*

Factor	Standard of care (n=654)	Pembrolizumab (n=647)	P-value
Sex			
Female	259 (40)	264 (41)	0.69
Male	295 (60)	383 (59)	
Age (years)	54 (18, 86)	53 (20, 82)	0.11
Age			
< 50 years	201 (31)	234 (36)	0.057
50 to < 65 years	272 (41)	263 (41)	
≥ 65 years	181 (28)	150 (23)	
Body-mass index			
< 25	151 (23)	154 (24)	0.68
25 to < 30	231 (35)	239 (37)	
≥ 30	272 (42)	254 (39)	
Standard of care group choice (pre-randomization)			
High dose interferon	154 (24)	153 (24)	0.81
Ipilimumab	465 (71)	454 (70)	
High dose interferon pre-choice	35 (5)	40 (6)	
Disease stage (AJCC v7)			
Stage IIIA (N2a)	58 (9)	71 (11)	0.59
Stage IIIB	353 (54)	336 (52)	
Stage IIIC	208 (32)	209 (32)	
Stage IV	35 (5)	31 (5)	
Type of lymph node involvement			
Macroscopic	280 (43)	281 (43)	0.81
Microscopic	269 (41)	271 (42)	
Not reported	105 (16)	95 (15)	
Number of positive lymph nodes			
0	8 (1)	7 (1)	0.48
1	249 (38)	224 (35)	
2 or 3	208 (32)	223 (34)	
4 or more	85 (13)	99 (15)	
Not reported	104 (16)	94 (15)	
Ulceration			
Yes	257 (39)	245 (38)	0.83
No	266 (41)	274 (42)	
Unknown	131 (20)	128 (20)	
PD-L1 expression status ¶			

Factor	Standard of care (n=654)	Pembrolizumab (n=647)	P-value
Positive	536 (82)	534 (82)	0.66
Negative	93 (14)	94 (15)	
Indeterminate	25 (4)	19 (3)	
BRAF mutation status [#]			
Wild type	174 (27)	171 (26)	1
Mutated	138 (21)	138 (22)	
Unknown	343 (52)	338 (52)	

[*] No significant difference was detected in comparing the two groups.

[¶] PD-L1 staining was performed centrally before randomization on tumor biopsy from the primary or metastatic site

[#] *BRAF* mutation status was determined by the testing available to the local institution and was not required by the protocol, but was collected where available.

Table 2.

Adverse events with a frequency of 10% or greater in any category, determined to be related to the treatment by the treating physician; reported among patients who received protocol therapy.

To be included in the safety analysis, patients must have received at least one dose of protocol therapy (n=1204). Adverse event severity was scored using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

	Pembrolizumab (n=639)		**Ipilimumab (n=420)**		**High-dose Interferon (n=145)**	
	Any Grade	**Grade 3–5**	**Any Grade**	**Grade 3–5**	**Any Grade**	**Grade 3–5**
Any (regardless of treatment attribution)	**628 (98%)**	**204 (32%)**	**415 (99%)**	**240 (57%)**	**145 (100%)**	**105 (72%)**
Any related to treatment	**583 (91%)**	**111 (17)**	**401 (95%)**	**179 (43%)**	**143 (99%)**	**96 (66%)**
Led to Discontinuation	**108 (17%)**	**108 (17%)**	**272 (65%)**	**272 (65%)**	**36 (25%)**	**36 (25%)**
Lead to Death	**2 (<1%)**	**2 (<1%)**	**2 (<1%)**	**2 (<1%)**	**0**	**0**
Toxicities observed in > 10% of patients any grade						
Fatigue	374 (59%)	3 (<1%)	214 (51%)	13 (3%)	127 (88%)	17 (12%)
Rash - maculo-papular	187 (29%)	9 (1%)	183 (44%)	31 (7%)	27 (19%)	0
Diarrhea	144 (23%)	18 (3%)	200 (48%)	51 (12%)	63 (43%)	3 (2%)
Hypothyroidism	135 (21%)	0	56 (13%)	2 (<1%)	10 (7%)	0
AST increased	110 (17%)	14 (2%)	92 (22%)	18 (4%)	101 (70%)	15 (10%)
Arthralgia	109 (17%)	3 (<1%)	31 (7%)	3 (1%)	35 (24%)	1 (1%)
ALT increased	95 (15%)	19 (3%)	108 (26%)	24 (6%)	97 (67%)	20 (14%)
Myalgia	72 (11%)	1 (<1%)	29 (7%)	3 (1%)	53 (37%)	2 (1%)
Anemia	55 (9%)	1 (<1%)	36 (9%)	1 (<1%)	40 (28%)	0
Anorexia	50 8%)	1 (<1%)	74 (18%)	2 (<1%)	78 (54%)	0
Lymphocyte count decreased	46 (7%)	3 (<1%)	8 (2%)	0	35 (24%)	14 (10%)
Abdominal pain	34 (5%)	2 (<1%)	60 (14%)	5 (1%)	20 (14%)	1 (1%)
Dizziness	27 (4%)	0	27 (6%)	0	45 (31%)	1 (1%)
White blood cell count decreased	27 (4%)	0	6 (1%)	0	83 (57%)	20 (14%)
Hypertriglyceridemia	25 (3.9%)	1 (0.2%)	8 (1.9%)	0	18 (12.3%)	8 (5.5%)
Colitis	18 (3%)	13 (2%)	52 (12%)	35 (8%)	0	0
Neutrophil count decreased	14 (2%)	2 (<1%)	14 (3%)	0	91 (63%)	51 (35%)
Anxiety	9 (1%)	0	8 (2%)	0	16 (11%)	2 (1%)

	Pembrolizumab (n=639)		Ipilimumab (n=420)		High-dose Interferon (n=145)	
	Any Grade	Grade 3–5	Any Grade	Grade 3–5	Any Grade	Grade 3–5
Depression	8 (1%)	0	5 (1%)	0	26 (18%)	4 (3%)