European Journal of Cancer 158 (2021) 156–168

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

Crossover and rechallenge with pembrolizumab in recurrent patients from the EORTC 1325-MG/Keynote-054 phase III trial, pembrolizumab versus placebo after complete resection of high-risk stage III melanoma☆

Alexander MM. Eggermont [a,*], Andrey Meshcheryakov [b], Victoria Atkinson [c], Christian U. Blank [d], Mario Mandala [e,ae], Georgina V. Long [f,af], Catherine Barrow [g], Anna Maria Di Giacomo [h], Rosalie Fisher [i,ag], Shahneen Sandhu [j], Ragini Kudchadkar [k], Pablo Luis Ortiz Romero [l], Inge Marie Svane [m], James Larkin [n], Susana Puig [o], Peter Hersey [p], Pietro Quaglino [q], Paola Queirolo [r,ah], Daniil Stroyakovskiy [s], Lars Bastholt [t], Peter Mohr [u], Micaela Hernberg [v], Vanna Chiarion-Sileni [w], Matthew Strother [x], Axel Hauschild [y], Naoya Yamazaki [z], Alexander CJ. van Akkooi [d], Paul Lorigan [aa], Clemens Krepler [ab], Nageatte Ibrahim [ab], Sandrine Marreaud [ac], Michal Kicinski [ac,1], Stefan Suciu [ac,1], Caroline Robert [ad,1]

[a] *Princess Máxima Center and University Medical Center Utrecht, Utrecht, 3584 CS, the Netherlands*
[b] *Federal State Budgetary Institution "Russian Oncology Scientific Centre named after N.N. Blokhin RAMS", Moscow, Russia*
[c] *Princess Alexandra Hospital, University of Queensland, Brisbane, Australia*
[d] *Netherlands Cancer Institute – Antoni van Leeuwenhoek, Amsterdam, the Netherlands*
[e] *Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy*
[f] *Melanoma Institute Australia, The University of Sydney, Sydney, Australia*
[g] *Wellington Hospital, Wellington, New Zealand*
[h] *Center for Immuno-Oncology, University Hospital of Siena, University of Siena, Siena, Italy*
[i] *North Shore Hospital, Waitemata DHB, Takapuna, Auckland, New Zealand*
[j] *Peter Maccallum Cancer Centre, Melbourne, Australia*
[k] *Emory University, Atlanta, GA, USA*
[l] *Hospital 12 de Octubre, Institute i+12, CIBERONC, Medical School, University Complutense, Madrid, Spain*
[m] *Herlev Hospital, University Copenhagen, Herlev, Denmark*
[n] *Royal Marsden Hospital - Chelsea, London, United Kingdom*
[o] *Hospital Clinic Universitari de Barcelona, Barcelona, Spain*
[p] *David Maddison Clinical Sciences, Gateshead, Australia*

☆ This study is registered with ClinicalTrials.gov, NCT02362594, and EudraCT, 2014-004944-37.

* *Corresponding author.*
E-mail address: alexander.eggermont@prinsesmaximacentrum.nl (A.MM. Eggermont).

[1] Contributed equally to this paper.

https://doi.org/10.1016/j.ejca.2021.09.023

[q] Azienda Ospedaliera Città della Salute e della Scienza di Torino, Ospedale San Lazzaro, Torino, Italy
[r] Istituto Nazionale Per La Ricerca Sul Cancro, Genova, Italy
[s] Municipal Oncology Hospital 62, Krasnogorskiy, Russia
[t] Odense University Hospital, Odense, Denmark
[u] Elbe Kliniken, Buxtehude, Germany
[v] Helsinki University Central Hospital, Helsinki, Finland
[w] Azienda Ospedaliera Di Padova, Padova, Italy
[x] Christchurch Hospital, Christchurch, New Zealand
[y] Universitaetsklinikum Schleswig-Holstein, Campus Kiel - Klinik Dermatologie, Venerologie und Allergologie, Kiel, Germany
[z] National Cancer Center Hospital, Chuo-ku, Japan
[aa] The University of Manchester and Christie NHS Foundation Trust, Manchester, UK
[ab] Merck & Co., Inc., Kenilworth, NJ, USA
[ac] EORTC Headquarters, Brussels, Belgium
[ad] Gustave Roussy Cancer Campus Grand Paris and University Paris-Saclay, Villejuif, France
[ae] Ospedale Santa Maria Della Misericordia, Perrugia, Italy
[af] Mater and Royal North Shore Hospitals, Sydney, Australia
[ag] Auckland City Hospital, Auckland, New Zealand
[ah] European Institute of Oncology IRCCS, Milan, Italy

Received 28 September 2021; accepted 28 September 2021
Available online 19 October 2021

KEYWORDS
Melanoma;
anti–PD-1;
Pembrolizumab;
Salvage treatment

Abstract ***Background:*** In the phase III double-blind European Organisation for Research and Treatment of Cancer 1325/KEYNOTE-054 trial, pembrolizumab improved recurrence-free and distant metastasis-free survival in patients with stage III cutaneous melanoma with complete resection of lymph nodes. In the pembrolizumab group, the incidence of grade I–V and of grade III–V immune-related adverse events (irAEs) was 37% and 7%, respectively.
Methods: Patients were randomised to receive intravenous (i.v.) pembrolizumab 200 mg (N = 514) or placebo (N = 505) every 3 weeks, up to 1 year. On recurrence, patients could enter part 2 of the study: pembrolizumab 200 mg i.v. every 3 weeks up to 2 years, for crossover (those who received placebo) or rechallenge (those who had recurrence ≥6 months after completing 1-year adjuvant pembrolizumab therapy). For these patients, we present the safety profile and efficacy outcomes.
Results: At the clinical cut-off (16-Oct-2020), in the placebo group, 298 patients had a disease recurrence, in which 155 (52%) crossed over ('crossover'). In the pembrolizumab group, 297 patients completed the 1-year treatment period; 47 had a recurrence ≥6 months later, in which 20 (43%) entered the rechallenge part 2 ('rechallenge').

In the crossover group, the median progression-free survival (PFS) was 8.5 months (95% confidence interval [CI] 5.7–15.2) and the 3-year PFS rate was 32% (95% CI 25–40%). Among 80 patients with stage IV evaluable disease, 31 (39%) had an objective response: 14 (18%) patients with complete response (CR) and 17 (21%) patients with partial response. The 2-year PFS rate from response was 69% (95% CI 48–83%). In the rechallenge group, the median PFS was 4.1 months (95% CI 2.6–NE). Among 9 patients with stage IV evaluable disease, 1 had an objective response (CR). Among the 175 patients, 51 (29%) had a grade I–IV irAE and 11 (6%) had a grade III–IV irAE.
Conclusions: Pembrolizumab treatment after crossover yielded an overall 3-year PFS rate of 32% and a 39% ORR in evaluable patients, but the efficacy (11% ORR) was lower in those rechallenged.

1. Introduction

In the last 2 decades or so, new drugs have been tested in advanced [1,2] and adjuvant setting melanoma. Ipilimumab [3–5], nivolumab [6,7] and pembrolizumab [8–13] were tested in patients with melanoma at high risk for relapse regardless of BRAF mutation status, and dabrafenib plus trametinib combination [14–16] was assessed in BRAF-mutant patients. US Food and Drug Administration approved all these drugs, and

European Medicine Agency (EMA) approved all but ipilimumab. The ipilimumab [3–5], pembrolizumab [8–13] and dabrafenib plus trametinib [14–16] trials were conducted in patients with lymph-node resected stage III disease, including also patients with higher-risk stage IIIA disease (the diameter of the micro-metastasis had to be >1 mm, as per the Rotterdam criteria of Sentinel Node (SN)-tumour load) [17–19]. In the same vein, the Checkmate-238 nivolumab trial was conducted in patients with stage III B–C disease and in patients with resected stage IV disease [6,7].

A unique aspect of the European Organisation for Research and Treatment of Cancer (EORTC) 1325/KEYNOTE-054 trial is the crossover or rechallenge design that enables patients in the placebo arm and pembrolizumab arm (patients who had recurrence ≥6 months after completing adjuvant therapy with pembrolizumab) to be unblinded at relapse and then offered treatment with pembrolizumab for up to 2 years in part 2 of the study. This unique design allows us to report on the response rate and progression-free survival (PFS) rates in treatment-naïve patients and in pembrolizumab pre-treated patients who were rechallenged with pembrolizumab at relapse. Here, we report for the first time on the results obtained in part 2 of the EORTC 1325/KEYNOTE-054 trial.

2. Patients and methods

2.1. Study design and patients

This double-blind, randomised, controlled, phase III trial was carried out at 123 academic centres and community hospitals across 23 countries. The study design is indicated in the Supplementary Fig. A. 1. In part 1 of the study, patients who were 18 years of age or older with histologically confirmed cutaneous melanoma metastatic to regional lymph nodes were eligible to enter the study. Patients had either stage IIIA melanoma (patients with N1a or N2a had to have at least one micrometastasis measuring >1 mm in greatest diameter) or stage IIIB or IIIC disease with no in-transit metastases as per the AJCC-7 classification [8,20]. We also reported on all patients who were restaged as per AJCC-8 classification [9,21]. Complete regional lymphadenectomy was required within 13 weeks of commencing of treatment. The exclusion criteria included Eastern Cooperative Oncology Group (ECOG) performance status score of 2–4, presence of autoimmune disease, presence of uncontrolled infections, the use of systemic corticosteroids and prior systemic therapy for melanoma. A tumour sample from melanoma-positive lymph nodes was required to be sent for central pathology evaluation of PD-L1 expression [8,22].

Registration was carried out centrally at the EORTC headquarters. The randomisation was stratified by AJCC-7 staging and region [8]. Only the local pharmacists were aware of trial group assignments. Patients were randomly assigned in a 1:1 ratio to receive either an intravenous infusion of pembrolizumab 200 mg or placebo every 3 weeks for a total of 18 doses for ~1 year or until disease recurrence, unacceptable toxicity, major protocol violation or withdrawal of consent.

Patients who experienced a disease recurrence and met the inclusion criteria (i.e. lack of evidence of brain metastases and an ECOG performance status of 0–2) had the possibility to enter part 2 of the study (Supplementary Fig. A.1). Among patients initially randomised to the pembrolizumab arm, only those with a recurrence later than 6 months from the completion of the whole year of treatment were eligible for entering part 2 of the study. In this second part, patients received pembrolizumab 200 mg intravenously every 3 weeks for a maximum of two years. Treatment in part 2 was terminated at the time of a disease progression as per Response Evaluation Criteria in Solid Tumours (RECIST) 1.1 or when treatment toxicity or intercurrent illness warranted the patient's withdrawal from study treatment. For patients with a local recurrence before entry in part 2, the treatment could be stopped at either 1 or 2 years, at the discretion of the investigator.

2.2. End-points and assessments

Information as provided by the local investigators was used to calculate the end-points. PFS was defined as the time from the start of pembrolizumab in part 2 of the study until the date of progression (as per RECIST 1.1), disease recurrence or death from any cause. For patients with stage III disease with no evidence of disease, recurrence-free survival (RFS) was defined as the time from the start of pembrolizumab in part 2 of the study until the date of first recurrence (local, regional or distant metastasis) or death from any cause. As a measure of the duration of response, PFS was computed from the date of reaching partial response (PR) or complete response (CR), whichever occurred first, until the date of first progression/recurrence or death from any cause. For patients without any event, the follow-up was censored at the latest disease evaluation performed as per the protocol.

In patients who entered part 2 of the study, computed tomography or magnetic resonance imaging of the chest, abdomen and pelvis was performed every 12 weeks from the start of crossover or rechallenge treatment until disease progression, recurrence or completion of treatment. Disease assessments after the end of treatment were performed as per the standard practice of the participating hospitals.

For patients with a measurable stage IV disease at the baseline, the best response was assessed as per RECIST 1.1.

The severity of adverse events (AEs) was graded as per the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The AEs were reported between the first dose and 30 days after the last dose; for serious AEs and immune-related AEs (irAEs), a time limit of 90 days after the last dose was used.

The study protocol was approved by the EORTC protocol review committee and independent ethics committees. The study was conducted in accordance with the Declaration of Helsinki and with Good Clinical Practice as defined by the International Conference on Harmonisation. All patients eligible for part 2 of the study provided written informed consent before entry into part 2 of the study.

The trial was monitored by the EORTC independent data and safety monitoring committee. On-site source data verification was provided by a clinical research organisation.

2.3. Statistical analysis

For part 1 of the study, details regarding sample size computations, implementation of an interim analysis in an amended protocol and the dissemination of the treatment outcome results were provided in the original publication [8]. At 1.25-year median follow-up, pembrolizumab prolonged RFS from randomisation in the total population (hazard ratio 0.57, 98.4% confidence interval [CI] 0.43–0.74) [8]. This improvement was confirmed at 3- and 3.5-year median follow-up evaluations [11,12]. As the rate of recurrence in part 1 decreased over time, the recruitment of patients in part 2 declined as well reaching less than 1 patient per month in 2020. Therefore, the Study Steering Committee decided to define the clinical cut-off date for the first evaluation of outcomes in part 2 of the study on 16th October 2020. The database lock for this analysis took place on 17th December 2020.

PFS and RFS distributions were estimated using the Kaplan-Meier method, and the 95% CI for the rates was obtained via the Greenwood variance formula. The median estimates of PFS and RFS and their two-sided 95% CI were computed as per the Brookmeyer and Crowley method. Time to CR and time to objective response distributions were estimated using the Aalen-Johansen estimator with going off-protocol treated as a competing event.

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

3. Results

3.1. Patient groups: characteristics

At the time of the clinical cut-off, among 505 patients randomised to the placebo arm, 298 patients had disease recurrence, of which 155 (51.8%) participated in the crossover part of the trial ('crossover' group). Of these 155 patients, 105 patients had advanced disease (95 with stage IV disease and 10 with unresected stage III disease) and 50 had stage III fully resected locoregional recurrence at the time of crossover.

Among 514 patients randomised to the pembrolizumab arm, 297 patients completed the whole year of adjuvant treatment after a resection of a high-risk stage III melanoma and 47 patients had a disease recurrence 6 months or more from the completion of one year of adjuvant treatment, of which 20 (42.6%) participated in the rechallenge part of the trial: 13 patients with stage IV disease and 7 patients with stage III disease with a fully resected locoregional recurrence at the baseline of rechallenge.

The characteristics of patients who crossed over or underwent rechallenge as per the initial stage at the start of part 2 are provided in Table 1 and Supplementary Table A.1. The part 2 baseline characteristics by M category among 105 patients with advanced disease at the time of crossover are provided in Supplementary Table A.2.

3.2. Treatment applicability and reason for discontinuation

The median number of doses of pembrolizumab was 12 (interquartile range [IQR] 5–29) among the 155 patients who crossed over and 5.5 (IQR 3.5–20) among the 20 patients who were rechallenged (Supplementary Table 3). The median treatment duration in part 2 was 8 months (IQR 2.8–20.3) among the 155 patients who crossed over and 3.2 months (IQR 1.7–13.7) among the 20 patients who were rechallenged.

At the time of the clinical cut-off, out of 175 patients included in part 2, 15 (8.6%) patients were on treatment, 24 (13.7%) patients completed the treatment, and 136 (77.7%) patients discontinued the treatment, including 87 (49.7%) patients who discontinued the treatment due to disease progression or recurrence and 20 (11.4%) patients who discontinued the treatment due to toxicity. The distribution of patients as per the group and stage at the start of part 2 is provided in Table 2.

3.3. Outcomes of crossover patients ('crossover' group)

For the 155 patients who crossed over from placebo, the median follow-up time was 41 months (IQR 30–48). The median PFS was 8.5 months (95% CI: 5.7–15.2), and the PFS rate at 3 years from the start of pembrolizumab treatment in part 2 was 32.2% (95% CI: 24.5–40.2%) (Supplementary Fig. A.2).

For the 105 patients with advanced disease who crossed over from placebo, the median PFS was 8.2 months (95% CI: 5.3–15.2), and the 3-year PFS rate was 32.0% (95% CI: 22.8–41.6%) (Fig. 1A). Fig. 1B

Table 1
Patients' characteristics by group and stage at part 2 baseline.

	Crossover (N = 155)		Rechallenge (N = 20)		
	Advanced disease (N = 105)	Stage III resected (N = 50)	Advanced disease (N = 13)	Stage III resected (N = 7)	Total (N = 175)
	N (%)	N (%)	N (%)	N (%)	N (%)
Age, years					
<50	31 (29.5)	18 (36.0)	5 (38.5)	2 (28.6)	56 (32.0)
50–64	34 (32.4)	22 (44.0)	5 (38.5)	4 (57.1)	65 (37.1)
65+	40 (38.1)	10 (20.0)	3 (23.1)	1 (14.3)	54 (30.9)
Sex					
Male	71 (67.6)	26 (52.0)	8 (61.5)	5 (71.4)	110 (62.9)
Female	34 (32.4)	24 (48.0)	5 (38.5)	2 (28.6)	65 (37.1)
BRAF mutation status at randomisation to adjuvant treatment					
Wild type	41 (39.0)	22 (44.0)	6 (46.2)	3 (42.9)	72 (41.1)
V600 E/K mutation	54 (51.4)	22 (44.0)	6 (46.2)	2 (28.6)	84 (48.0)
Other	7 (6.7)	4 (8.0)	1 (7.7)	1 (14.3)	13 (7.4)
Unknown	3 (2.9)	2 (4.0)	0 (0.0)	1 (14.3)	6 (3.4)
ECOG performance status					
0	96 (91.4)	49 (98.0)	13 (100.0)	7 (100.0)	165 (94.3)
1	7 (6.7)	1 (2.0)	0 (0.0)	0 (0.0)	8 (4.6)
2	2 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.1)
LDH					
N	102 (97.1)	50 (100.0)	13 (100.0)	7 (100.0)	172 (98.3)
≤ULN	78 (76.5)	40 (80.0)	9 (69.2)	6 (85.7)	133 (77.3)
>ULN-2xULN	21 (20.6)	9 (18.0)	4 (30.8)	1 (14.3)	35 (20.3)
>2xULN	3 (2.9)	1 (2.0)	0 (0.0)	0 (0.0)	4 (2.3)
Disease status at the baseline					
Stage III, unresected*, following	10* (9.6)	49 (98.0)	0 (0)	7 (100.0)	66 (37.7)
Local recurrence	0 (0.0)	15 (30.0)	0 (0.0)	5 (71.4)	20 (11.4)
In transit metastasis	5 (4.8)	16 (32.0)	0 (0.0)	1 (14.3)	22 (12.6)
Regional lymph nodes positive	5 (4.8)	18 (36.0)	0 (0.0)	1 (14.3)	24 (13.7)
Stage IV	95 (90.5)	0 (0)	13 (100.0)	0 (0)	108 (61.7)
Stage IV resected	12 (11.4)	0 (0)	4 (30.8)	0 (0)	16 (9.1)
Stage IV unresected	83 (79.0)	0 (0)	9 (69.2)	0 (0)	92 (52.6)
AJCC-8 M1a	22 (21.0)	0 (0.0)	4 (30.8)	0 (0.0)	26 (14.9)
AJCC-8 M1b	36 (34.3)	0 (0.0)	5 (38.5)	0 (0.0)	41 (23.4)
AJCC-8 M1c	36 (34.3)	0 (0.0)	4 (30.8)	0 (0.0)	40 (22.9)
AJCC-8 M1d	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Second primary melanoma	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Time from randomisation to adjuvant treatment and recurrence before part 2, years					
N	105 (100.0)	49 (98.0)	13 (100.0)	7 (100.0)	174 (99.4)
0–<1	72 (68.6)	32 (65.3)	1 (7.7)	0 (0.0)	105 (60.3)
1–<2	24 (22.9)	12 (24.5)	7 (53.8)	1 (14.3)	44 (25.3)
2+	9 (8.6)	5 (10.2)	5 (38.5)	6 (85.7)	25 (14.4)

Patients with advanced disease include those with stage IV or unresected stage III disease.
ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; N, number of patients; ULN, upper limit of normal.

indicates the PFS outcome as per the AJCC-8 M status at the start of treatment.

There were 25 patients considered not evaluable for response to treatment. Ten patients had unresected stage III disease at the baseline, and 12 had distant metastases, but these were fully resected (Table 1). In addition, 4 patients had insufficient/inadequate follow-up (1 patient with a fully resected metastasis also had insufficient follow-up).

In the remaining subset of 80 patients who had an evaluable response, the median PFS was 6.1 months (95% CI: 4.1–15.2), and the 3-year PFS rate was 30.9% (95% CI: 20.9–41.5%) (Fig. 2A). Among these 80 patients, there were 31 (39%) patients who achieved an objective response: 14 (18%) achieved a CR, and 17 (21%) achieved a PR (Table 3). Most of the PRs were reported at the first disease evaluation performed at week 12 (Supplementary Fig. A3), whereas the CRs were reported to occur mostly within 15 months from the start of the treatment (Supplementary Fig. A.4). For the 31 responders, the PFS rate at two years from objective response was 68.7% (95% CI: 48.0–82.5%), and at 3 years, it was approximately 50% (Fig. 2B). Among the 13 patients who reached CR, two had a

Table 2
Reasons for treatment discontinuation by group and stage at part 2 baseline.

	Crossover (N = 155)		Rechallenge (N = 20)		
	Advanced disease (N = 105)	Stage III resected (N = 50)	Advanced disease (N = 13)	Stage III resected (N = 7)	Total (N = 175)
	N (%)	N (%)	N (%)	N (%)	N (%)
Normal completion	16 (15.2)	7 (14.0)	1 (7.7)	0 (0.0)	24 (13.7)
Recurrence/progression/death due to PD	53 (50.5)	23 (46.0)	8 (61.5)	3 (42.9)	87 (49.7)
Adverse event	11 (10.5)	8 (16.0)	1 (7.7)	0 (0.0)	20 (11.4)
The patient's/investigator's decision not AE related	12 (11.4)	7 (14.0)	1 (7.7)	1 (14.3)	21 (12.0)
Recurrence/progression and new malignancy	0 (0.0)	1 (2.0)	0 (0.0)	0 (0.0)	1 (0.6)
Lost to follow-up	1 (1.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)
Other	5 (4.8)	1 (2.0)	0 (0.0)	0 (0.0)	6 (3.4)
On-treatment	7 (6.7)	3 (6.0)	2 (15.4)	3 (42.9)	15 (8.6)

PD, progressive disease; AE, adverse event.
Patients with advanced disease include those with stage IV or unresected stage III disease.

recurrence at the time of cut-off, and one died because of an unknown cause, after a non–drug-related AE.

Among the 50 patients who crossed over from placebo and had a fully resected locoregional recurrence at the baseline of crossover, the median RFS was 13.6 months (95% CI: 5.3–27.3). The RFS rate at 3 years from the start of crossover treatment was 33.2% (95% CI: 19.8–47.2%) (Fig. 1A).

3.4. Outcomes of rechallenged patients ('rechallenge' group)

For the 20 patients who were rechallenged with pembrolizumab, the median follow-up time was 19 months (IQR 14–26). For these patients, the median PFS was 4.1 months (95% CI, 2.6–not estimable) (Fig. 3A). Among the 13 patients with stage IV disease, 9 (69%) had a disease progression within 14 months from the start of rechallenge and 4 patients had follow-up exceeding 16 months and were alive and progression-free at the time of the clinical cut-off (Fig. 3B). Among 9 patients with stage IV disease evaluable for response, one reached CR, 3 patients were considered stable disease and 5 as progressive disease.

Among 7 rechallenged patients with resected stage III melanoma, 3 had a loco-regional recurrence, of whom one developed a distant metastasis as well.

3.5. Safety

Among 175 patients who started the treatment, 51 had a grade I–IV irAE: 25 (14%) patients had hypothyroidism, 17 (10%) patients had hyperthyroidism, 5 (3%) patients had hypophysitis, 3 (2%) patients had type 1 diabetes mellitus, 3 (2%) patients had pneumonitis or interstitial lung disease, 4 (2%) patients had vitiligo, 3 (2%) patients had colitis, 2 patients had pancreatitis, 1 patient had adrenal insufficiency, 1 patient had hepatitis and 1 patient had myositis (Table 4). Most irAEs occurred within the first year from the start of part 2 (Supplementary Fig. A.5). In the crossover and rechallenge groups, respectively, 47 (30%) patients of 155 and 4 (20%) of 20 reported an irAE. Overall, there were 11 (6%) patients who had a grade III–IV irAE, all in the crossover group. No grade V AEs have been reported.

4. Discussion

Herein, we report the efficacy and safety results of two patient populations in part 2 of the EORTC 1325/KEYNOTE-054 adjuvant trial in patients with high-risk stage III melanoma who received pembrolizumab after recurrence. Patients in the placebo arm who relapsed were offered pembrolizumab at 200 mg for up to 2 years or progression by trial design. These patients are expected to have response rates and a PFS as observed in treatment-naïve patients with advanced melanoma as observed in the KEYNOTE-006 [23] and Checkmate-067 [24] trials and recently compiled in a comprehensive review [25]. This was indeed the case in our trial: the median PFS was 8.5 months (95% CI 5.7–15.2), and the 3-year PFS rate was 32% (95% CI 25–40%). Among 80 patients with stage IV evaluable disease, 31 (39%) had an objective response: 14 (18%) patients had CR, and 17 (21%) patients had PR. The 2-yr PFS rate from response was 69% (95% CI 48–83%). The second group of patients that, by trial design, was offered pembrolizumab at recurrence was that which had recurrence ≥6 months after having completed 1 year of adjuvant therapy with pembrolizumab. This group was enriched for innate or acquired anti–PD-1 resistance and for which limited data are currently available. In these patients, the median PFS was only 4.1 months (95% CI 2.6–NE), and

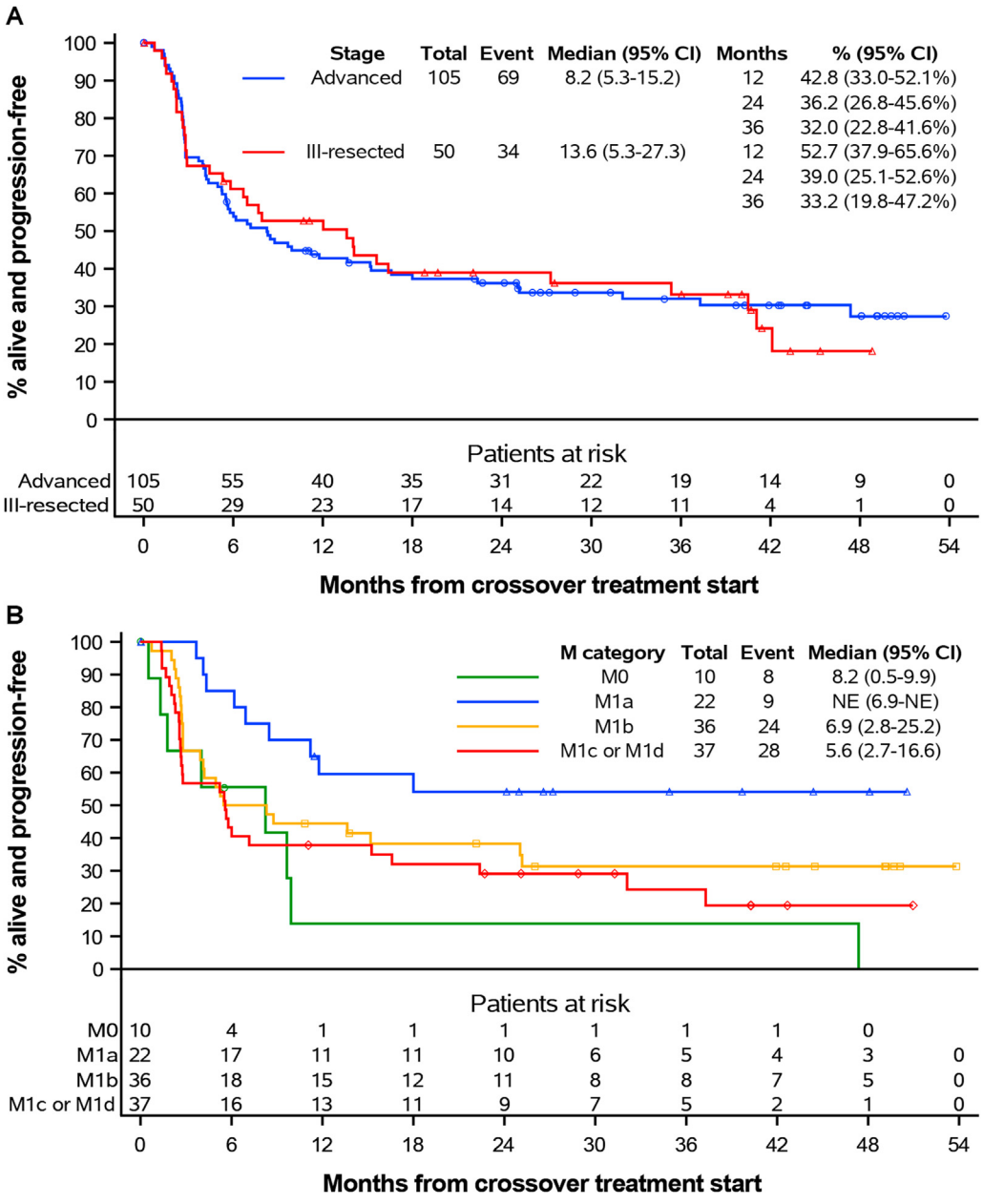

Fig. 1. **Progression-free survival in the crossover population by (A) stage of disease at the start of part 2 and (B) M staging in patients with stage IV or unresected stage III disease.** Patients with advanced disease include those with stage IV or unresected stage III disease. For patients with resected stage III disease, PFS represents RFS. The marks on the lines indicate the time of censoring. PFS, progression-free survival; RFS, recurrence-free survival; CI, confidence interval.

among the 9 patients with stage IV evaluable disease, only 1 patient (11%) had an objective response (CR). The one-year PFS rate of 41% was also clearly lower. Despite of small numbers, these lower response and PFS rates in patients who were rechallenged with pembrolizumab seem to indicate a distinct biology of this cohort of patients compared with treatment-naïve patients.

Owen et al. [26] reported on 20 similar patients who relapsed after having completed adjuvant anti–PD-1 therapy for stage III-BC/IV melanoma. Of these 20 patients, 2 of 5 patients responded to retreatment with PD-1 monotherapy, 2 of 5 patients responded to ipilimumab-based therapy (± PD-1 inhibitor) and 9 of 10 patients responded to BRAF/MEK inhibitors. The two patients who responded to anti–PD-1 retreatment had previously completed the 1-year adjuvant anti–PD-1 treatment; they had recurrence at 5.6 and 13.5 months later and on re-treatment maintained a response after 10.3 and 5.4 months of anti–PD-1

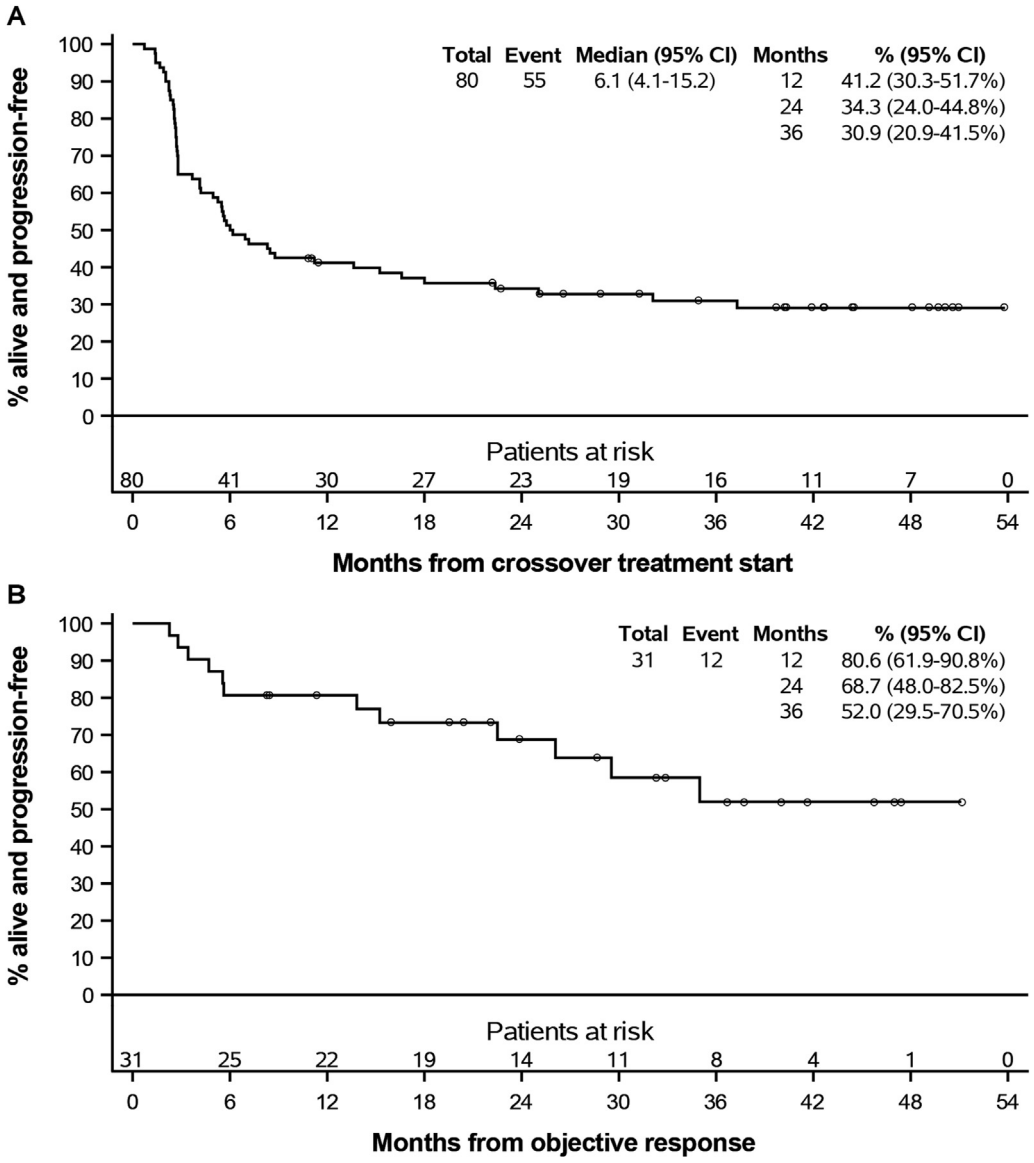

Fig. 2. **Progression-free survival among crossover patients evaluable for response (A) from the start of treatment; (B) from objective response in patients who reached CR or PR.** The circles indicate the time of censoring. CR, complete response; PR, partial response; CI, confidence interval.

treatment. Of 104 patients who had recurrence during adjuvant anti–PD-1, none (0/6) responded to anti–PD-1 alone; 8 of 33 evaluable patients (24%) responded to ipilimumab-based therapy (monotherapy or in combination with PD-1 inhibitors), and 18 of 23 (78%) responded to BRAF/MEK inhibitors. These findings led to the conclusion that there is no role for continued anti–PD-1 therapy but that there is a clear role for ipilimumab-based therapy (alone or combined with PD-1 inhibitors) and targeted therapy with BRAF/MEK inhibitors in patients who have recurrence during adjuvant anti–PD-1 monotherapy. Robert et al. [23] reported the retreatment of 5 patients with anti–PD-1 monotherapy after completion of adjuvant anti–PD-1 therapy, but there were 2 (durable) responders, which is favourable compared with the 1 responder of 9 patients in our EORTC 1325/KEYNOTE-054 current experience. Da Silva et al. [27]

Table 3
Best response as per the AJCC-8 staging in the crossover subgroup.

	M1a N = 14 (100%)	M1b N = 30 (100%)	M1c/M1d N = 36 (100%)	Total N = 80 (100%)
Response	10 (71.4)	8 (26.7)	13 (36.1)	31 (38.8)
Complete response	6 (42.9)	4 (13.3)	4 (11.1)	14 (17.5)
Partial response	4 (28.6)	4 (13.3)	9 (25.0)	17 (21.3)
Stable disease	2 (14.3)	11 (36.7)	8 (22.2)	21 (26.3)
Progressive disease	2 (14.3)	11 (36.7)	15 (41.7)	28 (35.0)

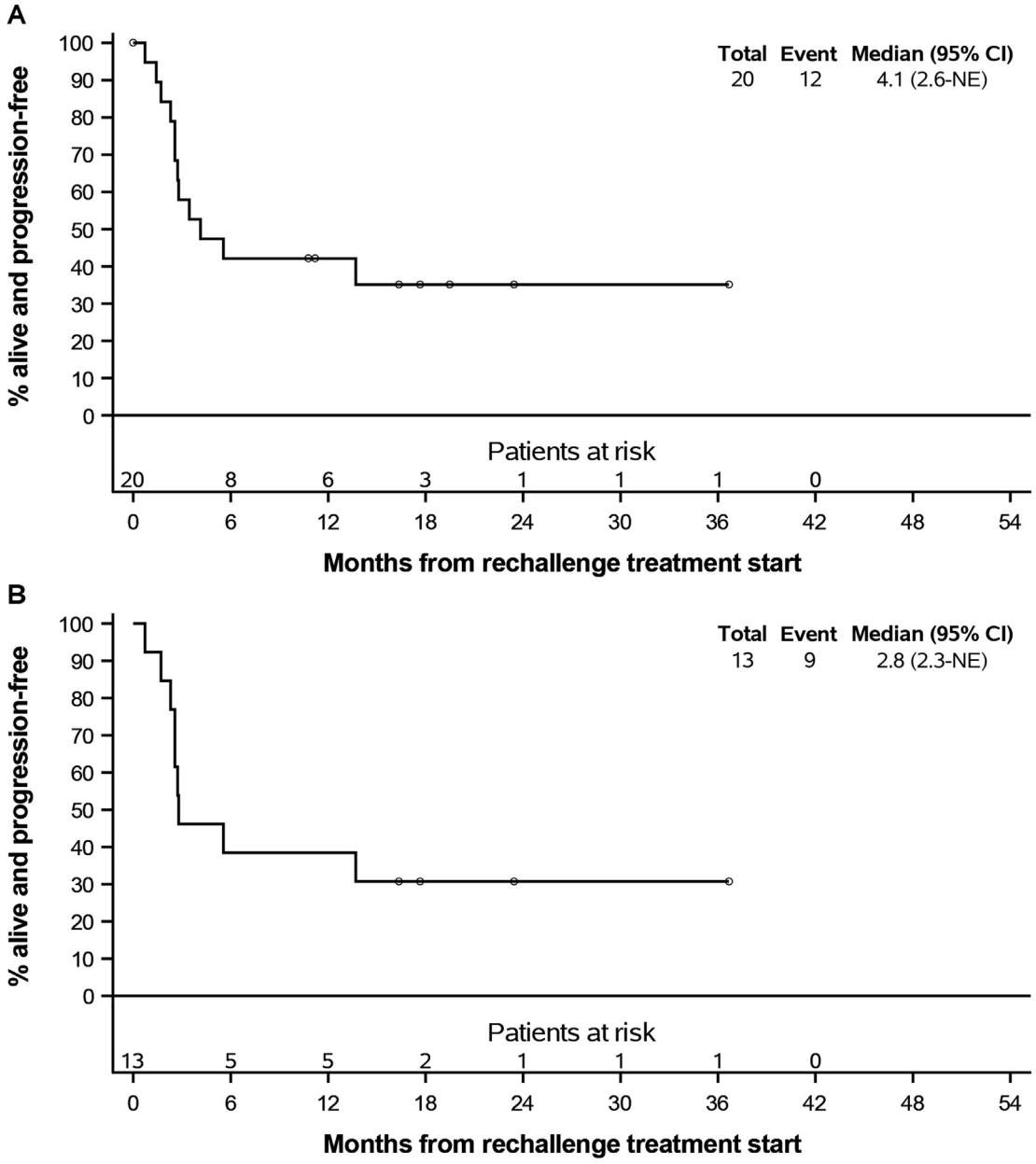

Fig. 3. **Progression-free survival for (A) all rechallenged patients and (B) rechallenged patients with advanced disease.** The circles indicate the time of censoring. CI, confidence interval.

assessed recurrences after adjuvant and non-adjuvant anti–PD-1 monotherapy. They did not report on retreatment with anti–PD-1 monotherapy but observed that of 44 of 355 (12.4%) patients with melanoma who progressed after adjuvant anti–PD-1 monotherapy, eight (18%) received ipilimumab and 36 (82%) received combined anti–PD-1 and ipilimumab. Responses occurred in 1 of 8 ipilimumab-treated patients (13%) and 13 of 36 (36%) patients treated with ipilimumab plus PD-1 inhibitors, indicating improved efficacy from the combination treatment in the setting of anti–PD-1 resistance [27].

Regarding side-effects, no unusual observations were made: among the 175 patients, 51 (29%) had a grade I–IV irAE (47 [30%] in the crossover group and 4 [20%] in the rechallenge group) and 11 (6%) had a grade III–IV irAE.

In conclusion, pembrolizumab treatment after crossover yielded an overall 3-yr PFS rate of 32% and a 39% ORR in evaluable patients, but after rechallenge, the

Table 4
Immune-related adverse events (irAEs) by group.

	Crossover (N = 155)		Rechallenge (N = 20)	
	Grade I–IV N (%)	Grade III–IV N (%)	Grade I–IV N (%)	Grade III–IV N (%)
Any irAE	47 (30.3)	11 (7.1)	4 (20.0)	0 (0.0)
Endocrine disorders	33 (21.3)	5 (3.2)	3 (15.0)	0 (0.0)
Hypothyroidism	22 (14.2)	0 (0.0)	3 (15.0)	0 (0.0)
Hyperthyroidism	17 (11.0)	1 (0.6)	0 (0.0)	0 (0.0)
Thyroiditis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Hypophysitis (including hypopituitarism)	5 (3.2)	1 (0.6)	0 (0.0)	0 (0.0)
Type 1 diabetes mellitus	3 (1.9)	3 (1.9)	0 (0.0)	0 (0.0)
Adrenal insufficiency	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory/thoracic disorders	3 (1.9)	2 (1.3)	0 (0.0)	0 (0.0)
Vitiligo or severe skin reactions	9 (5.8)	5 (3.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	5 (3.2)	2 (1.3)	0 (0.0)	0 (0.0)
Hepatobiliary disorders	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Other irAEs	2 (1.3)	0 (0.0)	1 (5.0)	0 (0.0)
Myositis	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)
Infusion reactions	1 (0.6)	0 (0.0)	1 (5.0)	0 (0.0)

efficacy was lower. In the latter group of patients, new strategies are needed to improve the outcome.

Funding

This work was supported by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Data sharing statement

Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA (MSD), is committed to providing qualified scientific researchers access to anonymised data and clinical study reports from the company's clinical trials for the purpose of conducting legitimate scientific research. MSD is also obligated to protect the rights and privacy of trial participants and, as such, has a procedure in place for evaluating and fulfilling requests for sharing company clinical trial data with qualified external scientific researchers. The MSD data sharing website (available at: http://engagezone.msd.com/ds_documentation.php) outlines the process and requirements for submitting a data request. Applications will be promptly assessed for completeness and policy compliance. Feasible requests will be reviewed by a committee of MSD subject matter experts to assess the scientific validity of the request and the qualifications of the requestors. In line with data privacy legislation, submitters of approved requests must enter into a standard data-sharing agreement with MSD before data access is granted. Data will be made available for request after product approval in the US and EU or after product development is discontinued. There are circumstances that may prevent MSD from sharing requested data, including country- or region-specific regulations. If the request is declined, it will be communicated to the investigator. Access to genetic or exploratory biomarker data requires a detailed, hypothesis-driven statistical analysis plan that is collaboratively developed by the requestor and MSD subject matter experts; after approval of the statistical analysis plan and execution of a data-sharing agreement, MSD either will perform the proposed analyses and share the results with the requestor or will construct biomarker covariates and add them to a file with clinical data that is uploaded to an analysis portal so that the requestor can perform the proposed analyses.

Author contributions

Alexander MM Eggermont: Conceptualisation, Methodology, Supervision, Writing-original draft preparation, Writing-review and editing; Andrey Meshcheryakov, Victoria Atkinson, Christian U Blank, Mario Mandala, Georgina V Long, Catherine Barrow, Anna Maria Di Giacomo, Rosalie Fisher, Shahneen Sandhu, Ragini Kudchadkar, Pablo Luis Ortiz Romero, Inge Marie Svane, James Larkin, Susana Puig, Peter Hersey, Pietro Quaglino, Paola Queirolo, Daniil Stroyakovskiy, Lars Bastholt, Peter Mohr, Micaela Hernberg, Vanna Chiarion-Sileni, Matthew Strother, Axel Hauschild, Naoya Yamazaki, Alexander CJ van Akkooi, Paul Lorigan: Resources (patients), Investigation, Writing-review and editing; Clemens Krepler, Nageatte Ibrahim: Project administration, medical review, Funding acquisition, Writing-review and editing. Sandrine Marreaud: Project administration, medical review, Writing-review and editing. Michal Kicinski: Methodology, Data Curation, Formal analysis, Visualisation, Writing-original draft preparation, Writing-review and editing. Stefan Suciu: Conceptualisation, Methodology, Visualisation, Writing-original draft preparation, Writing-review and editing. Caroline Robert: Resources (patients), Methodology, Investigation, Supervision, Writing-review and editing.

Conflict of interest statement

A.M.M.E.—consulting fees: Biocad, BioInvent, BioNTech, BMS, CatalYm, Ellipses, GSK, IO Biotech, ISA Pharmaceuticals, Merck/MSD, Nektar, Novartis, Pfizer, SAiRoPA, Sellas, SkylineDx, TigaTx, TTxDiscovery; payment or honoraria: Biocad, BMS, Merck/MSD, Novartis; payment for expert testimony: Novartis; support for attending meetings and/or travel: BMS; participation on a Data Safety Monitoring Board or Advisory Board: GSK, Novartis and Pfizer; leadership or fiduciary role in other board, society, committee or advocacy group, paid or unpaid: European Academy Cancer Sciences Gerrman Cancer Aid; stock or stock options: SkylineDx and SAiRoPA

P.L.—personal fees, advisory, speaker, trial grants: BMS, Merck, Novartis, GSK, Amgen, Chugai, Pierre Fabre, NeraCare, Roche and Oncology Education Canada.

N.I.—stock or stock options: Merck stock; other financial interest: employee Merck & Co.

M.K.—study funding from Merck to institution; grants or contacts: Pierre Fabre; sponsor and provider of an academic grant for different melanoma studies (money paid to the author's institution); BMS Sponsor and provider of an academic grant for different melanoma studies (money paid to the author's institution).

S.S.—Merck is the sponsor of this study; payment was made to the author's institution; grants or contracts: BMS, Pierre Fabre—sponsor and provider of academic grants to other EORTC melanoma studies; payments were made to the author's institution.

C.R.—consulting fees: occasional consultant for Roche, Novartis, Pierre Fabre, MSD, BMS, Sanofi, Pfizer; payment or honoraria: occasional consultant for Roche, Novartis, Pierre Fabre, MSD, BMS, Sanofi and Pfizer.

A.M.—grants or contracts: Merck Sharp Dohme Pharmaceuticals and Bristol Myers Squibb; payment or honoraria: Merck Sharp Dohme Pharmaceuticals and Bristol Myers Squibb; support for attending meetings: Merck Sharp Dohme Pharmaceuticals and Bristol Myers Squibb.

V.A.—payment or honoraria: BMS, MSD, Nektar, Novartis, Pierre Fabre, Q Biotics, Roche and Limbic Ad Boards.

C.K.—stock or stock options: Merck & Co.

C.B.—grants or contracts: BMS, Novartis and NanoString Payments were made to the author's institution; consulting fees: BMS, MSD, Roche, Novartis, Lilly, Pfizer, GSK, GenMab and Pierre Fabre; payments were made to the author's institution. Third Rock Venture: payments were made to the author; stock or stock options: Unity Cars—Stocks; Immagene BV - Co-founder.

A.C.J.v.A.—grants or contracts from any entity: Amgen, Merck-Pfizer, all paid to the institute and unrelated to current work; participation on a Data Safety Monitoring Board or Advisory Board: Amgen, Bristol Myers Squibb, Novartis, MSD-Merck, Merck-Pfizer, Pierre Fabre, Sanofi, Sirius Medical, 4SC, all paid to the institute and unrelated to current work

M.M.—payment or honoraria: BMS, MSD, Novartis, Pierre Fabre and Sanofi.

G.V.L. is a consultant advisor for Aduro Biotech Inc, Amgen Inc, Array Biopharma inc, Boehringer Ingelheim International GmbH, Bristol Myers Squibb, Hexel AG, Highlight Therapeutics S.L., Merck Sharpe & Dohme, Novartis Pharma AG, OncoSec, Pierre Fabre, QBiotics Group Limited, Regeneron Pharmaceuticals Inc, SkylineDX B.V., specialised Therapeutics Australia Pty Ltd; payment or honoraria: Bristol Myers Squibb—personal—one hour lecture of the author's own slides; Pierre Fabre—personal—one hour lecture of the author's own slides.

A.M.D.G.—payment or honoraria: BMS, MSD, Sanofi, Pierre Fabre; compensated educational activities; support for attending meetings and/or travel: Pierre Fabre and BMS; participation on a Data Safety Monitoring Board or Advisory Board: BMS, MSD, Pierre Fabre, Sanofi, Incyte, GSK and Novartis.

S.S.—grants or contracts from any entity: Advanced Accelerators Applications (a Novartis company), Amgen, Merck Sharp & Dohme, Merck Serono, Genentech, AstraZeneca; funding to the institution; consulting fees: Amgen, Merck Sharp & Dohme, Merck Serono, AstraZeneca and Bristol Myer Squibb (funding to the institution).

R.K.—consulting fees: Merck, Array/Pfizer, BMS and Regeneron; participation on a Data

Safety Monitoring Board or Advisory Board: Merck, Array/Pfizer, Regeneron and BMS

P.L.O.R.—patents planned, issued or pending: PLCG1 for T-cell lymphoma. Participation on a Data Safety Monitoring Board or Advisory Board: Novartis, Takeda, Kyowa, 4SC, Helsinn, Recordati Rare Diseases, Innate Pharma, MIRAGEN advisory boards; payments to the author, receipt of equipment, materials, drugs, medical writing, gifts or other services: MEDA (Viatris) support for the investigator-initiated clinical trial.

I.M.S.—all support for the present manuscript: MSD/EORTC partly covering of trial-associated expenses to the author's institution; consulting fees: MSD - Webpage text, personal fee; support for attending meetings and/or travel: MSD—Conference in oncology; participation on a Data Safety Monitoring Board or Advisory Board: Roche/Genentech—IDSM, personal fee, Pierre Fabre; Novartis—Adv board, personal fee.

S.P.—grants or contracts from any entity: Almirall—to the author's institution; ISDIN—to the author's institution; La Roche-Posay—to the author's

institution; consulting fees: ISDIN, Almirall—to the author; Sanofi, Sun Pharma—to the author; Pfizer, Roche and Regeneron—to the author; payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: ISDIN, La Roche-Posay—to the author; Pfizer, Roche and Regeneron—to the author. BMS, Sun Pharma—to the author; support for attending meetings and/or travel: Almirall—to the author; participation on a Data Safety Monitoring Board orAdvisory Board: Roche and Sanofi—to the author; Sun Pharma and Almirall—to the author; ISDIN, Pfizer and Novartis—to the author.

Pi.Q.—payment or honoraria: BMS, MSD, Pierre Fabre, Novartis and Roche; support for attending meetings and/or travel: BMS, MSD, Pierre Fabre, Novartis and Roche.

Pa.Q.—payment or honoraria: Roche, Novartis, Sun Pharma, Sanofi, BMS, MSD, Merck Serono and Pierre Fabre.

P.M.—payment or honoraria for lectures, presentations, speakers bureaus, manuscript writing or educational events: Amgen, Allmiral-Hermal, Beiersdorf, BMS, Medac, MSD, Pierre Fabre, Novartis, Roche and Sanofi Genzyme; support for attending meetings and/or travel: Amgen, Allmiral-Hermal, Beiersdorf, BMS, Medac, MSD, Pierre Fabre, Novartis, Roche and Sanofi Genzyme; participation on a Data Safety Monitoring Board or Advisory Board: CureVac AG.

M.H.—payment or honoraria: MSD, BMS, Novartis; lecture at MSD symposium; payment for expert testimony: Pierre Fabre—A written statement to the Finnish Pricing Board; Participation on a Data Safety Monitoring Board or Advisory Board: MSD, BMS, Novartis, Varian—Participation on National and Nordic advisory boards

A.H.—Grants or contracts from any entity: clinical trial support (grant to the institution): MSD/Merck, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma and Eisai; consulting fees: clinical trial support (grant to the institution): MSD/Merck, Philogen, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma and Eisai; Payment or honoraria: MSD/Merck, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma and Eisai; Participation on a Data Safety Monitoring Board or Advisory Board: MSD/Merck, Pierre Fabre, Regeneron, Roche, Sanofi-Genzyme, Novartis Pharma, Eisai, Immunocore, Replimune and Seagen.

N.Y.—grants or contracts from any entity: ONO Pharmaceuticals, Bristol Myers Squibb, Novartis Pharma K.K. , MSD K.K, Merck Serono Co., Ltd.; payment or honoraria: ONO Pharmaceuticals, Bristol-Myers Squibb, Novartis Pharma K.K. , MSD K.K., Merck Serono Co., Ltd. and Takeda Pharmaceutical Co., Ltd.

The other authors have no disclosures.

Acknowledgements

The authors are grateful to Merck & Co., Inc., Kenilworth, NJ, USA, for supporting this independent EORTC study. They thank all the investigators who participated in this study (Supplementary List A1). They warmly 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 (S. Janssen, R. Louis, N. Elaut, L. Wijnen, N. Jha, S Rivrain and G. de Schaetzen) as well as Merck & Co., Inc., Kenilworth, NJ, USA team members (V. Rivas, R. Kloss Silverman and S. Diede).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2021.09.023.

References

[1] Eggermont AMM, Spatz A, Robert C. Cutaneous melanoma. Lancet 2014;383:816–27.
[2] Ugurel S, Röhmel J, Ascierto PA, et al. Survival of patients with advanced metastatic melanoma: the impact of MAP kinase pathway inhibition and immune checkpoint inhibition - update 2019. Eur J Cancer 2020;130:126–38.
[3] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Adjuvant ipilimumab versus placebo after complete resection of high-risk stage III melanoma (EORTC 18071): a randomised, double-blind, phase 3 trial. Lancet Oncol 2015;16:522–30.
[4] Eggermont AM, Chiarion-Sileni V, Grob JJ, et al. Prolonged survival with Ipilimumab as adjuvant in stage III melanoma. N Engl J Med 2016;375:1845–55.
[5] Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. 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. Eur J Cancer 2019;119:1–10.
[6] Weber J, Mandala M, Del Vecchio M, et al. Adjuvant nivolumab versus ipilimumab in resected stage III or IV melanoma. N Engl J Med 2017;377:1824–35.
[7] Ascierto PA, Del Vecchio M, Mandalá M, et al. Adjuvant nivolumab versus ipilimumab in resected stage IIIB-C and stage IV melanoma (CheckMate 238): 4-year results from a multicentre, double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2020;21:1465–77.
[8] Eggermont AMM, Blank CU, Mandala M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma. N Engl J Med 2018;378:1789–801.
[9] Eggermont AMM, Blank CU, Mandala M, et al. Prognostic and predictive value of AJCC-8 staging in the phase III EORTC1325/KEYNOTE-054 trial of pembrolizumab vs placebo in resected high-risk stage III melanoma. Eur J Cancer 2019;116:148–57.
[10] Eggermont AMM, Kicinski M, Blank CU, et al. Association between immune-related adverse events and recurrence-free survival among patients with stage III melanoma randomized to receive pembrolizumab or placebo: a secondary analysis of a randomized clinical trial. JAMA Oncol 2020;6:519–27.
[11] Eggermont AMM, Blank CU, Mandala M, et al. Longer follow-up confirms recurrence-free survival benefit of adjuvant pembrolizumab in high-risk stage III melanoma: new results from the

EORTC 1325-MG/KEYNOTE-054 trial. J Clin Oncol 2020;38:3925–36.
[12] Eggermont AMM, Blank CU, Mandalà M, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): distant metastasis-free survival results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:643–54.
[13] Bottomley A, Coens C, Mierzynska J, et al. Adjuvant pembrolizumab versus placebo in resected stage III melanoma (EORTC 1325-MG/KEYNOTE-054): health-related quality-of-life results from a double-blind, randomised, controlled, phase 3 trial. Lancet Oncol 2021;22:655–64.
[14] Long GV, Hauschild A, Santinami M, et al. Adjuvant dabrafenib plus trametinib in stage III BRAF-mutated melanoma. N Engl J Med 2017;377:1813–23.
[15] Hauschild A, Dummer R, Schadendorf D, et al. Longer follow-up confirms relapse-free survival benefit with adjuvant dabrafenib plus trametinib in patients with resected BRAF V600-mutant stage III melanoma. J Clin Oncol 2018;36:3441–9.
[16] Dummer R, Hauschild A, Santinami M, et al. Five-year analysis of adjuvant dabrafenib plus trametinib in stage III melanoma. N Engl J Med 2020;383:1139–48.
[17] 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;248:49–55.
[18] 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.
[19] 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.
[20] Balch CM, Gershenwald JE, Soong SJ, et al. Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 2009;27:6199–206.
[21] Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67:472–92.
[22] Wolchok JD, Robert C, et al. Programmed death-ligand 1 expression and response to the anti-programmed death 1 antibody pembrolizumab in melanoma. J Clin Oncol 2016;34:4102–9.
[23] Robert C, Ribas A, Schachter J, et al. Pembrolizumab versus ipilimumab in advanced melanoma (KEYNOTE-006): post-hoc 5-year results from an open-label, multicentre, randomised, controlled, phase 3 study. Lancet Oncol 2019;20:239–51.
[24] Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med 2019;381:1535–46.
[25] Zaremba A, Eggermont AMM, Robert C, et al. The concepts of rechallenge and retreatment with immune checkpoint blockade in melanoma patients. Eur J Cancer 2021;155:268–80.
[26] Owen CN, Shoushtari AN, Chauhan D, et al. Management of early melanoma recurrence despite adjuvant anti-PD-1 antibody therapy. Ann Oncol 2020;31:1075–82.
[27] Pires da Silva I, Ahmed T, Reijers ILM, et al. Ipilimumab alone or ipilimumab plus anti-PD-1 therapy in patients with metastatic melanoma resistant to anti-PD-(L)1 monotherapy: a multicentre, retrospective, cohort study. Lancet Oncol 2021;22:836–47.