Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study

Georgina V Long, Reinhard Dummer, Omid Hamid, Thomas F Gajewski, Christian Caglevic, Stephane Dalle, Ana Arance, Matteo S Carlino, Jean-Jacques Grob, Tae Min Kim, Lev Demidov, Caroline Robert, James Larkin, James R Anderson, Janet Maleski, Mark Jones, Scott J Diede, Tara C Mitchell

Summary

Background Immunotherapy combination treatments can improve patient outcomes. Epacadostat, an IDO1 selective inhibitor, and pembrolizumab, a PD-1 inhibitor, showed promising antitumour activity in the phase 1–2 ECHO-202/KEYNOTE-037 study in advanced melanoma. In this trial, we aimed to compare progression-free survival and overall survival in patients with unresectable stage III or IV melanoma receiving epacadostat plus pembrolizumab versus placebo plus pembrolizumab.

Methods In this international, randomised, placebo-controlled, double-blind, parallel-group, phase 3 trial, eligible participants were aged 18 years or older, with unresectable stage III or IV melanoma previously untreated with PD-1 or PD-L1 checkpoint inhibitors, an ECOG performance status of 0 or 1, and had a known *BRAF*^{V600} mutant status or consented to *BRAF*^{V600} mutation testing during screening. Patients were stratified by PD-L1 expression and *BRAF*^{V600} mutation status and randomly assigned (1:1) through a central interactive voice and integrated web response system to receive epacadostat 100 mg orally twice daily plus pembrolizumab 200 mg intravenously every 3 weeks or placebo plus pembrolizumab for up to 2 years. We used block randomisation with a block size of four in each stratum. Primary endpoints were progression-free survival and overall survival in the intention-to-treat population. The safety analysis population included randomly assigned patients who received at least one dose of study treatment. The study was stopped after the second interim analysis; follow-up for safety is ongoing. This study is registered with ClinicalTrials.gov, number NCT02752074.

Findings Between June 21, 2016, and Aug 7, 2017, 928 patients were screened and 706 patients were randomly assigned to receive epacadostat plus pembrolizumab (n=354) or placebo plus pembrolizumab (n=352). Median follow-up was 12·4 months (IQR 10·3–14·5). No significant differences were found between the treatment groups for progression-free survival (median 4·7 months, 95% CI 2·9–6·8, for epacadostat plus pembrolizumab *vs* 4·9 months, 2·9–6·8, for placebo plus pembrolizumab; hazard ratio [HR] 1·00, 95% CI 0·83–1·21; one-sided p=0·52) or overall survival (median not reached in either group; epacadostat plus pembrolizumab *vs* placebo plus pembrolizumab: HR 1·13, 0·86–1·49; one-sided p=0·81). The most common grade 3 or worse treatment-related adverse event was lipase increase, which occurred in 14 (4%) of 353 patients receiving epacadostat plus pembrolizumab and 11 (3%) of 352 patients receiving placebo plus pembrolizumab. Treatment-related serious adverse events were reported in 37 (10%) of 353 patients receiving epacadostat plus pembrolizumab and 32 (9%) of 352 patients receiving placebo plus pembrolizumab. There were no treatment-related deaths in either treatment group.

Interpretation Epacadostat 100 mg twice daily plus pembrolizumab did not improve progression-free survival or overall survival compared with placebo plus pembrolizumab in patients with unresectable or metastatic melanoma. The usefulness of IDO1 inhibition as a strategy to enhance anti-PD-1 therapy activity in cancer remains uncertain.

Funding Incyte Corporation, in collaboration with Merck Sharp & Dohme.

Introduction

Advances in the development of immunotherapies, particularly immune checkpoint inhibitors that target PD-1, PD-L1, and CTLA-4, have greatly changed the treatment of advanced melanoma.[1–5] Ipilimumab, a CTLA-4 inhibitor, was the first checkpoint inhibitor to show improved overall survival in advanced melanoma.[3] However, the safety and tolerability profile of ipilimumab is not ideal, with approximately 60% of patients having immune-related adverse events.[3] Following this, two PD-1 inhibitors, pembrolizumab and nivolumab, showed improved survival benefits, durable responses, and a

Lancet Oncol 2019; 20: 1083–97

Published Online June 17, 2019 http://dx.doi.org/10.1016/S1470-2045(19)30274-8

See Comment page 1037

Melanoma Institute Australia, University of Sydney, Royal North Shore and Mater Hospitals, Sydney, NSW, Australia (Prof G V Long PhD); **Department of Dermatology, University Hospital Zürich, Zurich, Switzerland** (Prof R Dummer MD); **The Angeles Clinic and Research Institute, Los Angeles, CA, USA** (O Hamid MD); **Department of Pathology, University of Chicago Medical Center, Chicago, IL, USA** (Prof T F Gajewski MD); **Oncology Department, Clinica Alemana Santiago, Universidad del Desarrollo, Santiago, Chile** (C Caglevic MD); **Hospices Civils De Lyon, Cancer Research Center of Lyon, Claude Bernard University Lyon, Pierre Benite, France** (Prof S Dalle MD); **Medical Oncology, Hospital Clínic de Barcelona, Barcelona, Spain** (A Arance MD); **Westmead and Blacktown Hospitals, Melanoma Institute Australia, University of Sydney, Sydney, NSW, Australia** (M S Carlino PhD); **Service de Dermatologie et Cancérologie Cutanée, Aix-Marseille University, Marseille, France** (Prof J-J Grob MD); **Department of Haemato-Oncology, Seoul National University Hospital, Seoul, South Korea** (Prof T M Kim MD); **N N Blokhin Russian Cancer Research Center, Moscow, Russia** (Prof L Demidov MD); **Gustave Roussy Comprehensive Cancer Center, Villejuif, France** (Prof C Robert MD); **The Royal Marsden NHS Foundation**

Trust, London, UK (Prof J Larkin FRCP)**; Merck & Co, Inc, Kenilworth, NJ, USA** (J R Anderson PhD, S J Diede MD)**; Incyte Corporation, Wilmington, DE, USA** (J Maleski BSN, M Jones MD)**; and Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA, USA** (T C Mitchell MD)

Correspondence to: Prof Georgina V Long, Melanoma Institute Australia, University of Sydney, Sydney, NSW 2060, Australia
georgina.long@sydney.edu.au

Research in context

Evidence before this study

We searched PubMed on Aug 14, 2018, using the following search terms: (PD-1 OR "programmed death 1" OR PD-L1 OR "programmed death ligand" OR lambrolizumab OR pembrolizumab OR MK-3475 OR keytruda OR nivolumab OR BMS-936558 OR opdivo OR atezolizumab OR MPDL3280A OR JS-001 OR spartalizumab) AND (IDO1 OR IDO-1 OR IDO OR INDO OR indoleamine 2,3-dioxygenase OR epacadostat OR indoximod OR PF-06840003 OR KHK 2455 OR navoximod OR GED 0919 OR BMS-986205) AND melanoma. The search was limited to clinical trial publications, but no filters were set for date or language. No publications were identified reporting data from clinical studies of PD-1–PD-L1 and IDO1 inhibitor combinations in patients with advanced melanoma. However, before this phase 3 study, an open-label, phase 1–2 study (ECHO-202/KEYNOTE-037) assessing the efficacy and safety of epacadostat (25, 50, 100, or 300 mg twice daily doses in phase 1; 100 mg twice daily in phase 2) plus pembrolizumab (2 mg/kg or 200 mg every 3 weeks in phase 1; 200 mg once every 3 weeks in phase 2) in patients with various tumours, including advanced melanoma, was done in the USA. Although missing a comparator group, the results of this phase 1–2 study suggested that epacadostat plus pembrolizumab combination therapy was well tolerated, with 56% of patients with treatment-naive advanced melanoma (n=54) achieving an objective response, and might be a promising treatment for advanced melanoma.

Added value of this study

Our results showed no clinical benefit of epacadostat plus pembrolizumab compared with placebo plus pembrolizumab. To our knowledge, this was the first large randomised study across the field of immuno-oncology showing no further benefit from the addition of an immune agent other than anti-CTLA-4 to anti-PD-1 checkpoint inhibition.

Implications of all the available evidence

Epacadostat at the doses and schedule tested (100 mg twice daily) in this trial does not enhance the efficacy of pembrolizumab treatment alone.

lower incidence of grade 3 or worse adverse events compared with that of ipilimumab,[2,4] and have been approved for use in advanced melanoma globally.

Because tumour cells can use multiple mechanisms to evade immunosurveillance, combination treatment strategies targeting these mechanisms might be more effective at restoring immune function and improving clinical outcomes in patients with metastatic cancer. In patients with advanced melanoma,[4,5] combination treatment with nivolumab and ipilimumab was shown to improve objective response, progression-free survival, and overall survival compared with either ipilimumab or nivolumab alone. However, immune-related adverse events and systemic toxic effects were markedly higher with the combination therapy than with either monotherapy. Therefore, the need remains for an alternative treatment combination that improves overall survival without the burden of increased drug-related toxic effects.

IDO1 is an intracellular enzyme that catalyses the first and rate-limiting step of the tryptophan–kynurenine metabolism pathway, depleting local tryptophan concentrations and increasing concentrations of downstream metabolites, including kynurenine.[6] In the tumour microenvironment, decreased tryptophan and increased tryptophan metabolites induce cell-cycle arrest and effector T-cell apoptosis and promote regulatory T-cell activity, contributing to local immunosuppression.[6] IDO1 activation has been correlated with poor prognosis in patients with cancer,[7] including those with melanoma,[8] making it an attractive target for combination therapies using IDO1 inhibitors and PD-1 inhibitors. IDO1 and PD-L1 are commonly co-expressed in the tumour microenvironment of biopsies from patients with metastatic melanoma, with an increase in co-expression after immune therapy or targeted therapy[9] indicating a possible resistance mechanism. Furthermore, tumour IDO1 expression positively correlated with PD-L1 expression by melanoma cells in primary melanoma, locoregional metastasis, and distant metastasis specimens from patients with advanced melanoma,[10] supporting observations in mouse models that both proteins are upregulated by interferon gamma.[11]

In a preclinical melanoma mouse model,[12] the combination of an IDO inhibitor with a PD-L1 inhibitor resulted in more effective reactivation of anti-tumour immunity and tumour growth inhibition compared with that of either drug alone. Previous work[13] had established optimal activity of the selective IDO1 inhibitor epacadostat in in vivo models, with exposures that exceeded the half maximal inhibitory concentration at steady state, predose. These exposures were consistently reported in a phase 1 study[14] assessing the effects of epacadostat doses of 100 mg and higher, administered orally twice daily in patients with advanced solid tumours. However, in that study, no objective responses were reported for epacadostat monotherapy among 52 patients with several tumour types, including six patients with advanced melanoma.[14] By contrast, combination therapy with ipilimumab 3 mg/kg and epacadostat 50 mg twice daily resulted in four (22%) of 18 patients with immunotherapy-naive advanced melanoma achieving an objective response.[15] Data from the phase 1 portion of the ECHO-202 study,[16] assessing epacadostat and pembrolizumab in various solid tumours, reported that 11 (58%) of 19 patients with treatment-naive advanced melanoma achieved an objective response and found that this combination was well tolerated. The predominant epacadostat dose in this

report was 50 mg twice daily, but doses of 25–300 mg twice daily were also assessed; a formal analysis of dose–response effects was not done. The 100 mg twice daily dose of epacadostat was selected for phase 2 assessment in the ECHO-202 study because of its preliminary antitumour activity, favourable safety profile, preliminary phase 1 activity in melanoma, previous efficacy observed in melanoma with a 50 mg twice daily dose in combination with ipilimumab, and predicted target inhibition shown in phase 1 studies.[14–16] Two series of patients with melanoma treated with epacadostat and PD-1 inhibitors were subsequently reported. In two open-label, phase 1–2 studies[17,18] of patients with advanced melanoma, the combinations of epacadostat (100 mg twice daily) plus pembrolizumab (ECHO-202)[17] and epacadostat (100 mg or 300 mg twice daily) plus nivolumab (ECHO-204)[18] were well tolerated, with 18 (60%) of 30 (ECHO-202) and 26 (65%) of 40 (ECHO-204) patients naive to treatment achieving an objective response. The phase 3 ECHO-301/KEYNOTE-252 study was initiated to further assess the combination of epacadostat plus pembrolizumab in patients with unresectable or metastatic melanoma previously untreated with a checkpoint inhibitor. In this Article, we report efficacy and safety data from the ECHO-301 study.

Methods

Study design and participants

ECHO-301 was an international, randomised, placebo-controlled, double-blind, parallel-group, phase 3 trial done in 118 hospitals in 23 countries (appendix, pp 2–3). Eligible participants were aged 18 years or older who had histologically or cytologically confirmed, unresectable stage III or stage IV melanoma not amenable to local therapy; an ECOG performance status of 0 or 1; a known *BRAF*^{V600} mutation status or had consented to *BRAF*^{V600} mutation testing during screening; measurable disease in accordance with sponsor-modified Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (version 1.1 criteria, but with up to ten lesions and up to five lesions per organ [version 1.0 criteria] instead of up to five lesions and up to two lesions per organ [version 1.1 criteria]; cutaneous lesions and other superficial lesions were not deemed measurable lesions, but could be deemed non-target lesions); and no previous adjuvant therapy or treatment for advanced or metastatic disease, except for BRAF or MEK inhibitors (alone or in combination) for *BRAF*^{V600} mutant melanoma, previous adjuvant or neoadjuvant melanoma therapy if completed 4 weeks or longer before randomisation and all treatment-related adverse events either returned to baseline or stabilised, and previous adjuvant therapy containing immunotherapy (eg, interferon or anti-CTLA-4 therapy, excluding anti-PD1-based adjuvant therapy) if relapse did not occur during treatment or within 6 months of treatment discontinuation. Patients with previously treated brain metastases were eligible if the metastases were stable, with no evidence of new or enlarging brain metastases, and did not require steroid treatment up to 14 days before study treatment. Key exclusion criteria included previous treatment with IDO1 inhibitors or immune checkpoint inhibitors (except adjuvant CTLA-4 inhibitors, as described previously); an immunodeficiency or receipt of chronic systemic steroid therapy or any immunosuppressive therapy within 7 days of the first study treatment dose; autoimmune disease requiring systemic treatment in the past 2 years; active infection requiring systemic therapy; active central nervous system metastases; additional malignancy that was progressing or required active treatment; ocular melanoma; previous radiotherapy within 2 weeks of treatment initiation; previous monoclonal antibody therapy (except denosumab), chemotherapy, or treatment with an investigational drug or device within 4 weeks or 5 half-lives (whichever was longer) before administration of the study drug; known history of HIV, hepatitis B, hepatitis C, or steroid-requiring pneumonitis; or clinically significant cardiac disease (including unstable angina, acute myocardial infarction within 6 months of treatment initiation, New York Heart Association class III or class IV heart failure, and arrhythmia requiring treatment). Laboratory procedures or assessments that were done at screening included haematology, chemistry panels, urinalysis, pregnancy testing, hepatitis B and hepatitis C testing, haemostatic assessments, and endocrine monitoring (appendix, p 4).

On the basis of the results of the study, an external, independent data monitoring committee recommended that the study be stopped after the second interim analysis. The study was done in accordance with the protocol, Declaration of Helsinki, and International Council for Harmonisation guidelines for good clinical practice. The protocol (appendix p 15) and amendments were approved by the institutional review boards or independent ethics committees of participating institutions. All patients provided written informed consent.

See Online for appendix

Randomisation and masking

Patients were randomly assigned (1:1) to receive epacadostat plus pembrolizumab or placebo plus pembrolizumab by use of a central interactive voice and integrated web response system. We stratified randomisation by tumour PD-L1 status (PD-L1 positive *vs* PD-L1 negative or indeterminate) and *BRAF* mutation status (*BRAF* wild type *vs BRAF* mutant with previous *BRAF*-directed therapy *vs BRAF* mutant without previous directed therapy). We used block randomisation with a block size of four in each stratum. An external vendor (Almac, Craigavon, UK) handled randomisation, enrolment, and assignment. A double-blinding technique was used in which epacadostat and matching placebo were packaged identically. Patients, investigators, the study sponsors, and all study personnel involved in administering epacadostat or placebo or assessing outcomes were masked to group assignment. An independent, external data monitoring

committee monitored safety and efficacy. Patient-level emergent or medically necessary unmasking was restricted to an external unmasked statistician and scientific programmer who had no other study responsibilities.

Procedures

At the time the ECHO-301/KEYNOTE-252 phase 3 study was designed, safety data were available from 117 patients who had received epacadostat 100 mg twice daily in the phase 1 and 2 portions of the ECHO-202 trial; these data showed that this dose had a well tolerated safety profile in combination with pembrolizumab. On the basis of these observations, we selected epacadostat 100 mg twice daily for use in this phase 3 study. Patients received epacadostat 100 mg orally twice daily, or placebo, in combination with pembrolizumab 200 mg intravenously every 3 weeks. Patients could continue treatment for up to approximately 2 years (35 administrations of pembrolizumab) if they were benefiting from treatment and did not have disease progression or meet any criteria for study withdrawal. Treatment was discontinued for the following reasons: patient request; presence of a medical condition or patient circumstance that placed the patient at unnecessary risk during continued treatment; pregnancy; unacceptable adverse events (appendix p 5); progression or recurrence of any malignancy, or occurrence of another malignancy requiring treatment; intercurrent illness preventing further treatment; non-compliance; investigator decision; administrative reasons; or disease progression. Dose modifications were permitted to manage treatment-related adverse events and for specific situations unrelated to study treatment (eg, medical or surgical events or logistical reasons). The protocol provided dose modification guidelines for pembrolizumab for immune-related adverse events (appendix p 5) and infusion-related reactions associated with pembrolizumab. Infusions were to be stopped for grade 2 or worse infusion-related reactions, with permanent study drug treatment discontinuation for patients developing grade 2 adverse events despite adequate premedication and for patients developing grade 3 or grade 4 events. Epacadostat or matching placebo and pembrolizumab were to be immediately interrupted for patients exhibiting signs or symptoms of serotonin syndrome.

During treatment, haematology, chemistry panels, endocrine monitoring, and urinalysis were done beginning at cycle 2. Haemostatic testing was done according to standard of care or as clinically indicated at cycle 1, but not cycles 2 and 3. Urinalysis and endocrine monitoring were not done at cycle 3. Pregnancy testing was done 72 h before day 1 of each cycle and 30 days post treatment. For cycles 4 to 35, end of treatment, and safety follow-up, laboratory procedures were done according to standard of care or as clinically indicated. Predose laboratory procedures could be done up to 72 h before dosing.

We assessed safety and tolerability according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03, and by changes in laboratory parameters. All adverse events, including serious adverse events occurring from the time of treatment allocation or randomisation up to 90 days after cessation of treatment or if the patient initiated new anticancer therapy, whichever was earlier, were reported by the investigator. Adverse events of interest, on the basis of their probable immune cause, and infusion reactions were based on a list of terms specified by the funder and were considered by the investigators regardless of attribution to treatment or immune relatedness (appendix, p 6).

Tumour imaging was done by CT scan. MRI was used when CT was contraindicated or for brain imaging. Imaging was done up to 28 days before randomisation, at week 12, then every 9 weeks up to week 102, and then every 12 weeks until initial progressive disease according to sponsor-modified RECIST, version 1.1. Response was assessed by independent central review using sponsor-modified RECIST, version 1.1, and immune-related RECIST (irRECIST). Clinical progression was determined by investigators, with clinically stable disease defined as no decline in ECOG performance status, absence of new or worsening symptoms, absence of rapid progression of disease, and absence of progressive tumour at critical anatomical sites requiring urgent alternative medical intervention.

We used immunohistochemistry (PD-L1 IHC 22C3 PharmDx kit, Agilent Technologies, Santa Clara, CA, USA) to assess PD-L1 expression status. Positive PD-L1 status was defined as a melanoma score of 2 or higher (membrane PD-L1 expression in ≥1% of tumour cells or inflammatory cells in nests of tumour cells). Archival or fresh formalin-fixed, paraffin-embedded tissue samples were preferred but, if unavailable, freshly cut, unstained slides were permitted. IDO1 expression was assessed by use of in-situ hybridisation RNAscope technology (Advanced Cell Diagnostics, Newark, CA, USA).[19] In brief, *Homo sapiens* IDO1 mRNA probes were used to hybridise with target RNA in melanoma samples. Tissue sample types used were the same as those for the PD-L1 expression analyses. Each sample was quality controlled for RNA integrity with a probe specific to *PPIB* RNA and controlled for background with a probe specific to bacterial *dapB* RNA. Specific RNA staining signal was identified as red, punctate dots and slides were manually scored by a pathologist. IDO1 positivity was defined as tumour or intratumoural immune cell expression higher than 1% of cells. The physical testing of samples for IDO1 expression was retrospective: it was completed after the patients were enrolled and was not considered in the treatment assignment or primary analysis of the endpoints.

Outcomes

The primary endpoints were progression-free survival and overall survival. Progression-free survival was defined as the time from randomisation until the earliest date of disease progression (as determined

by sponsor-modified RECIST, version 1.1) or death from any cause, whichever came first. Overall survival was defined as the time from randomisation to death from any cause. Secondary endpoints included objective response, duration of response, safety, pharmacokinetics, and anti-pembrolizumab antibodies of epacadostat plus pembrolizumab therapy. Objective response was defined as a patient achieving a best response of either complete response or partial response. Duration of response was defined as the time from the earliest qualifying response (as determined by sponsor-modified RECIST, version 1.1) until the earliest disease progression or death from any cause, whichever came first. Exploratory endpoints included objective response, duration of response, and progression-free survival based on a sponsor-adapted version of irRECIST; analyses of study endpoints based on PD-L1 and IDO1 expression; ordinal categorical response score (complete response, very good response, minor response, stable disease, or progressive disease) at the final analysis; ordinal categorical response score at week 24; pharmacodynamics of epacadostat; and patient-reported outcomes. Analyses of pharmacokinetics, pharmacodynamics, and anti-pembrolizumab antibodies were not done because patients were unmasked and sample collections and planned analyses were discontinued after the interim analysis; therefore, these analyses are not presented here. Analyses of patient-reported outcomes were also not done because the primary endpoint was not met and unmasking occurred; therefore, these are not presented here. Analyses of irRECIST and ordinal categorical response scores at week 24 and final analysis were not done after the primary endpoint was not met. These analyses will not be subsequently reported elsewhere.

Statistical analysis

The planned sample size was approximately 700 patients. During the study, the planned patient enrolment was increased from 600 to 700 patients for three reasons. First, when screening was stopped, patients in screening were allowed to continue the screening process if consent was already given, and a large number of these patients were enrolled. Second, the assumed distributions for progression-free survival and overall survival were updated from exponential distributions to a cure-rate model that reduced the expected number of events, thereby necessitating an increase in sample size. Third, Japan was allowed to enrol additional patients to do a consistency analysis in Japanese patients for potential filing in Japan. Three efficacy analyses were planned for this trial. The first interim analysis was due to be done when approximately 331 progression-free survival events were observed, whereas the second interim analysis was due when 420 progression-free survival events were observed. The second interim analysis was to be the final progression-free survival analysis. The final overall survival analysis was due to be done after approximately 293 deaths had occurred. The overall type I error was controlled at 2·5% (one-sided) for the multiple endpoints tested (mathematically equivalent to a two-sided symmetric 5% level). An initial α of 1·25% (one-sided) was allocated to the progression-free survival analysis. The study had approximately 98% power to detect a hazard ratio (HR) of 0·65 favouring epacadostat over placebo. The analysis plan for progression-free survival assumed for the placebo plus pembrolizumab group was the following: median progression-free survival was 4·75 months, the distribution of progression-free survival was exponential for 70% of patients, and 30% of patients remained alive and progression free over the study follow-up period. An initial α of 1·25% (one-sided) was allocated to the overall survival analysis. The study had approximately 79% power to detect a HR of 0·70 for overall survival favouring epacadostat over placebo. The analysis plan for overall survival assumed for the placebo plus pembrolizumab group was the following: median overall survival was 14·00 months, the distribution of overall survival was exponential for 65% of patients, and 35% of patients remained alive over the study follow-up period. Treatment comparisons for progression-free survival and overall survival were assessed with use of a stratified log-rank test (stratified by PD-L1 status and $BRAF^{V600}$ mutation status). HR estimations were done with a Cox regression model. Event incidence over time was estimated within each treatment group with the Kaplan-Meier method. Efficacy was assessed in the intention-to-treat population, which consisted of all patients who were randomly assigned; safety was assessed in the population consisting of all patients who received one or more doses of the study drug. We did subgroup analyses of progression-free survival, overall survival, and objective response rate for prespecified subgroups determined by gender, age, race, disease stage, baseline ECOG status, $BRAF^{V600}$ mutation status, baseline lactate hydrogenase concentrations, and PD-L1 status, as well as a post-hoc subgroup determined by IDO1 status. The cutoff date for this analysis was Jan 8, 2018; only events that occurred before this date were included in this analysis.

Protocol modifications (initiated on Jan 25, 2017) affecting the original statistical design of the study included changes to the number and timing of interim analyses and adjustment of interim monitoring boundaries, as described in the appendix (p 1). We used SAS software (version 9.4) for the statistical analyses. This trial is registered with ClinicalTrials.gov, number NCT02752074.

Role of the funding source

The sponsor of the study designed the trial with assistance from a steering committee comprised of academic investigators and with input from the US Food and Drug Administration and the European Medicines Agency. The sponsor aided in data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

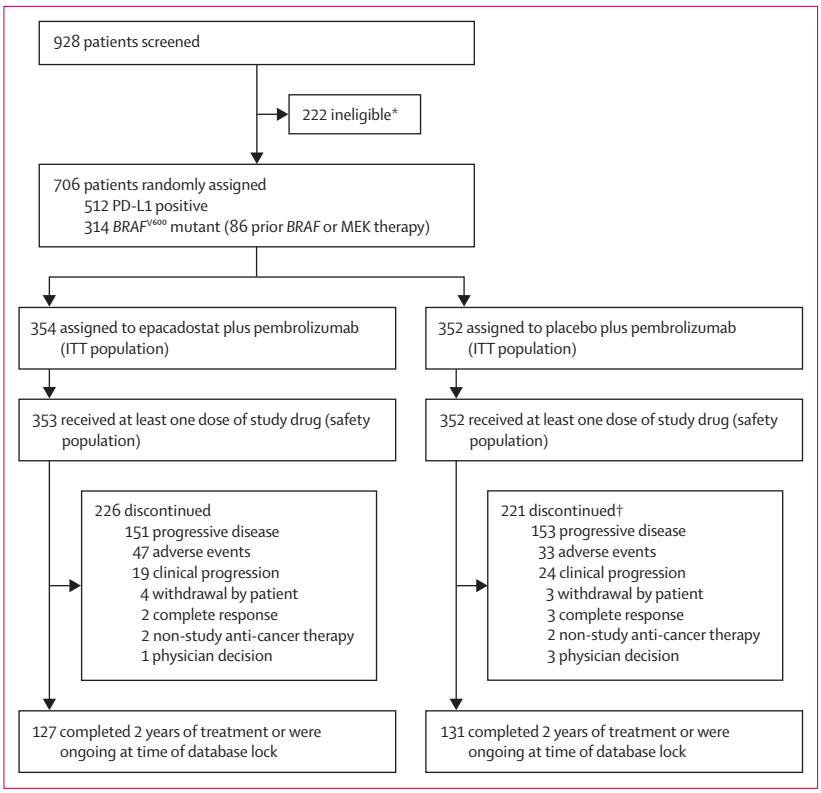

Figure 1: **Trial profile**
ITT=intention to treat. *Screening failures listed in the appendix (p 7). †Two patients discontinued placebo but continued receiving pembrolizumab

	Epacadostat plus pembrolizumab (n=354)	Placebo plus pembrolizumab (n=352)
Age, median (IQR), years	64 (52–72)	63 (53·5–72)
Sex		
Men	217 (61%)	206 (59%)
Women	137 (39%)	146 (41%)
Race		
White	311 (88%)	315 (89%)
Asian	40 (11%)	36 (10%)
Other or missing	3 (1%)	1 (<1%)
ECOG performance status		
0	261 (74%)	267 (76%)
1	93 (26%)	85 (24%)
Lactate dehydrogenase		
>ULN	123 (35%)	113 (32%)
>ULN but <2 times ULN	99 (28%)	93 (26%)
≥2 times ULN	24 (7%)	20 (6%)
M stage		
M0	14 (4%)	16 (5%)
M1a	39 (11%)	43 (12%)
M1b	73 (21%)	79 (22%)
M1c	228 (64%)	214 (61%)
Treated brain metastasis	19 (5%)	14 (4%)
Previous adjuvant or neoadjuvant therapy	34 (10%)	23 (7%)
Previous lines of therapy for advanced disease		
1	47 (13%)	37 (11%)
2 or more	1 (<1%)	5 (1%)
BRAF^{V600} status		
BRAF wild type	196 (55%)	196 (56%)
BRAF^{V600} mutant, previous directed treatment	43 (12%)	43 (12%)
BRAF^{V600} mutant, no previous directed treatment	115 (32%)	113 (32%)
PD-L1 status		
Positive	257 (73%)	255 (72%)
Negative	97 (27%)	97 (28%)
IDO1 status		
Positive*	219 (62%)	232 (66%)
Negative	28 (8%)	23 (7%)
Indeterminate	107 (30%)	97 (28%)

Data are n (%) unless otherwise specified. ULN=upper limit of normal. *Defined as 1% or higher tumour or intratumoural IDO1 expression.

Table 1: **Baseline characteristics of the intention-to-treat population**

Results

Between June 21, 2016, and Aug 7, 2017, we enrolled and randomly assigned 706 patients to treatment with epacadostat plus pembrolizumab (n=354) or placebo plus pembrolizumab (n=352; appendix p 7), from a total of 928 patients who were initially screened (figure 1). These 706 patients comprised the intention-to-treat population. Baseline characteristics were similar between treatment groups (table 1). Among all enrolled patients, the median age was 64 years (IQR 53–72). IDO1 expression was positive in 451 (90%) of 502 patients with evaluable tumour specimens. The staining for both tumour and intratumoural immune populations in terms of proportion of positive cells, as well as staining intensity, was balanced between the two groups in the study (table 1). The high proportion of IDO1-positive samples was mainly attributable to the staining of immune cells, where 422 (89%) of 472 samples were positive at the 1% or higher threshold. For tumour cells, 393 (78%) of 502 samples were positive at the 1% or higher threshold. IDO1 positivity was observed in both immune cells and tumour cells at the 1% threshold in 364 (77%) of 472 samples. Further analysis showed a high degree of overlap between the IDO1-positive and the PD-L1-positive populations, with 361 (72%) of 502 samples positive for both IDO-1 and PD-L1, when using the 1% cutoff value for both assays.

At data cutoff (Jan 8, 2018), with a median follow-up of 12·4 months (IQR 10·3–14·5), 226 (64%) of 354 patients in the epacadostat plus pembrolizumab group and 219 (62%) of 352 patients in the placebo plus pembrolizumab group had discontinued all treatment (additionally, two patients discontinued placebo because of adverse events [one with grade 2 anxiety and one with grade 2 pneumonitis] but remained on pembrolizumab after adverse event resolution; figure 1).

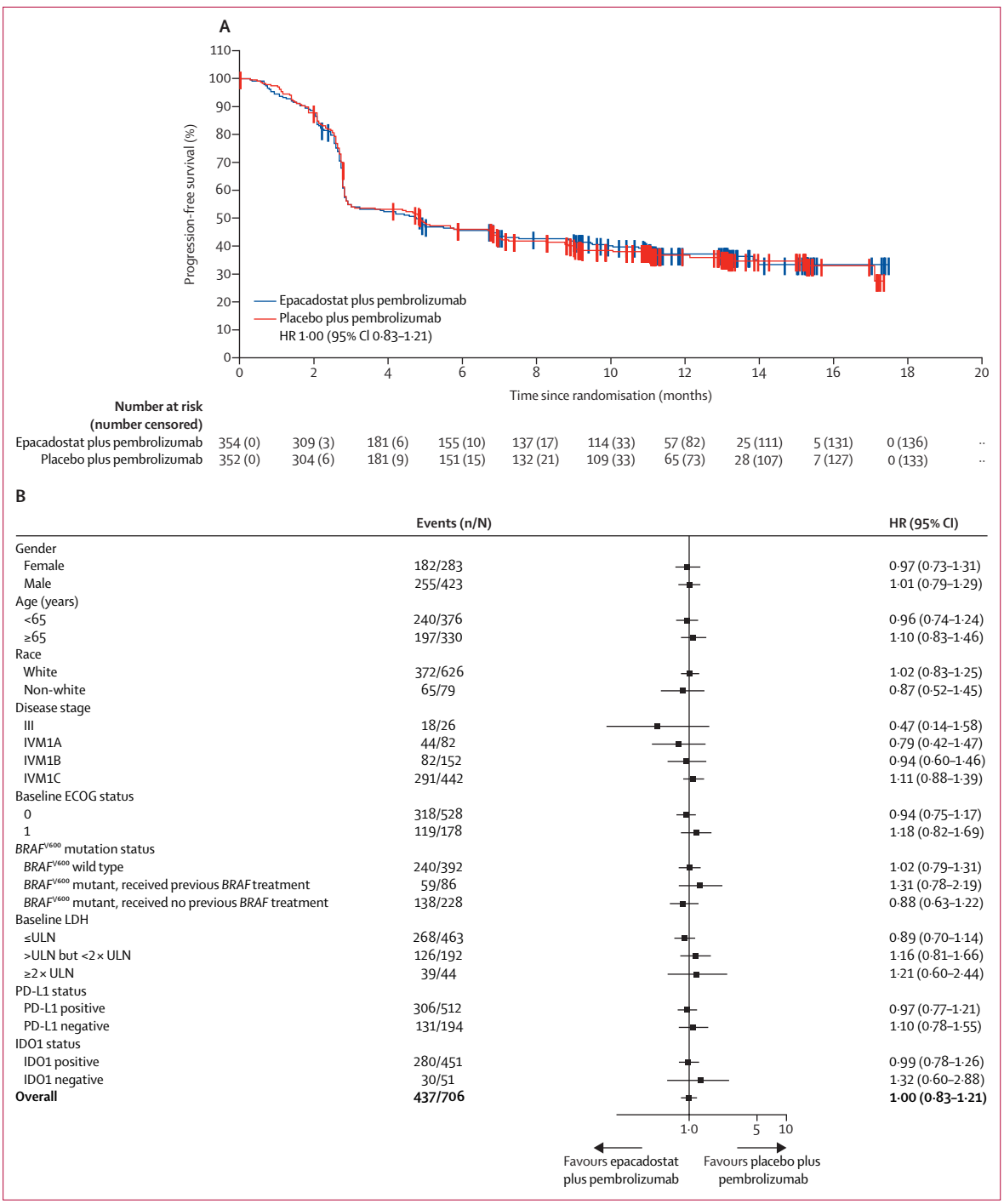

Figure 2: **Kaplan-Meier curves (A) and subgroup analyses (B) of progression-free survival**
Progression-free survival defined by sponsor-modified Response Evaluation Criteria In Solid Tumors, version 1.1. All subgroups were prespecified, except IDO1 status. HR=hazard ratio. LDH=lactate dehydrogenase. ULN=upper limit of normal.

As of data cutoff, 437 of 706 patients had a progression-free survival event (218 [62%] of 354 patients in the epacadostat plus pembrolizumab group and 219 [62%] of 352 patients in the placebo plus pembrolizumab group), which triggered the final analysis of progression-free survival. We observed no significant difference in progression-free survival between the two treatment groups, with a median progression-free survival of 4·7 months (95% CI 2·9–6·8) in the epacadostat plus pembrolizumab group and 4·9 months (2·9–6·8) in the

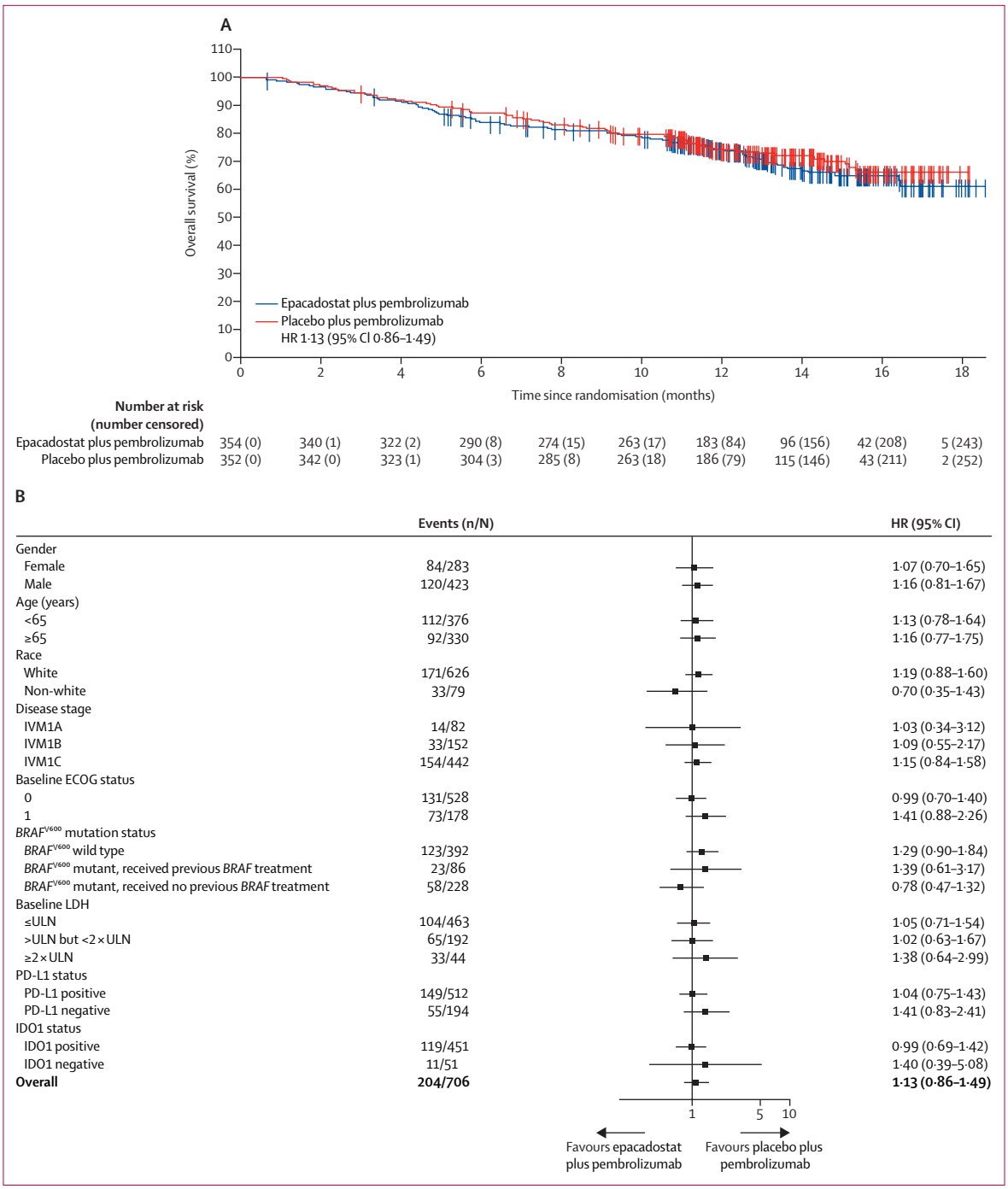

Figure 3: **Kaplan-Meier curves (A) and subgroup analyses (B) of overall survival**
All subgroups were prespecified, except IDO1 status groups, and only subgroups with five events or more are displayed in the figure. HR=hazard ratio. LDH=lactate dehydrogenase. ULN=upper limit of normal.

placebo plus pembrolizumab group (HR 1·00, 95% CI 0·83–1·21; one-sided p=0·52; figure 2A). In both groups, the progression-free survival at 6 months was 45·8% (95% CI 40·4–50·9 for epacadostat plus pembrolizumab, 40·5–51·0 for placebo plus pembrolizumab). The progression-free survival at 12 months was 36·9% (95% CI 31·7–42·2) in the epacadostat plus pembrolizumab group and 36·6% (31·4–41·9) in the placebo plus pembrolizumab group. The absence of a significant progression-free survival benefit for epacadostat was evident in all prespecified and post-hoc subgroups examined (figure 2B).

At the time of the final analysis of progression-free survival, the overall survival data were not yet mature, but there were 204 deaths (106 [30%] deaths in 354 patients in the epacadostat plus pembrolizumab group and 98 [28%] in 352 patients in the placebo plus pembrolizumab group), an event number sufficient for an interim analysis of overall survival according to protocol-specified criteria. Median overall survival was not reached in either group (figure 3). The HR for overall survival comparing epacadostat plus pembrolizumab versus placebo plus pembrolizumab was 1·13 (0·86–1·49; one-sided p=0·81). The overall survival was 84·1% (79·8–87·5) at 6 months and 74·4% (69·4–78·7) at 12 months in the epacadostat plus pembrolizumab group and 87·2% (83·2–90·3) at 6 months and 74·1% (69·0–78·5) at 12 months in the placebo plus pembrolizumab group. We found no significant differences between treatment groups for overall survival in any subgroup examined (figure 3).

Because the primary objective of prolonged progression-free survival or overall survival with epacadostat and pembrolizumab combination versus placebo plus pembrolizumab was not met, and because of the strong likelihood that the overall survival comparison would not be significant at the time of the pre-planned final overall survival analysis, the independent, external data monitoring committee recommended that the study be stopped. On the basis of this recommendation, all patients were unmasked, epacadostat and placebo administrations were stopped, and patients were switched to open-label pembrolizumab 200 mg once every 3 weeks (completing treatment up to a total of 35 total administrations of pembrolizumab). Therefore, the interim analysis of overall survival became the only analysis of overall survival; no additional efficacy analyses of the ECHO-301/KEYNOTE-252 trial beyond this interim analysis are planned.

Similar proportions of patients achieved an objective response in both study groups, with 14 (4%) of 354 patients in the epacadostat plus pembrolizumab group and 15 (4%) of 352 patients in the placebo plus pembrolizumab group achieving a complete response (table 2). We found no difference in objective response between treatment groups in any subgroup (appendix p 14). The median time to response was 2·8 months (IQR 2·7–2·9) in the epacadostat plus pembrolizumab group and 2·8 months (2·7–3·0) in the placebo plus pembrolizumab group. The median duration of response was not reached in either the epacadostat plus pembrolizumab group (IQR not reached–not reached) or the placebo plus pembrolizumab group (14·5 months–not reached). With a median time on epacadostat or placebo of 209 days (IQR 84–370) for patients in the epacadostat plus pembrolizumab group and 215 days (89–378) for patients in the placebo and pembrolizumab group, few responding patients lost response at the time of the analysis (15 [12%] of 121 patients in the epacadostat plus pembrolizumab group and 12 [11%] of 111 patients in the placebo plus pembrolizumab group). Disease control was similar between the two treatment groups (table 2).

	Epacadostat plus pembrolizumab (n=354)	Placebo plus pembrolizumab (n=352)
Objective response	121 (34%)	111 (32%)
Complete response	14 (4%)	15 (4%)
Partial response	107 (30%)	96 (27%)
Stable disease	59 (17%)	68 (19%)
Disease control*	180 (51%)	179 (51%)
Progressive disease	151 (43%)	150 (43%)
Non-complete response and non-progressive disease	10 (3%)	9 (3%)
Not available or assessable†	13 (4%)	14 (4%)

Data are n (%). Best response defined according to sponsor-modified Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. *Disease control defined as a patient achieving complete response, partial response, or stable disease. †Patient had no post-baseline imaging or had post-baseline imaging and the best objective response was determined to be non-assessable according to RECIST, version 1.1.

Table 2: **Best response to treatment**

Of 706 patients enrolled, 353 patients in the epacadostat plus pembrolizumab group and 352 patients in the placebo plus pembrolizumab group received at least one dose of study treatment and were assessed for safety (figure 1). One of 354 patients in the epacadostat plus pembrolizumab group died before receiving study treatment and was thus ineligible for the safety analysis. Any-grade adverse events occurred in 346 (98%) of 353 patients in the epacadostat plus pembrolizumab group and 345 (98%) of 352 patients in the placebo plus pembrolizumab group. Any serious adverse event was reported in 85 (24%) patients treated with epacadostat plus pembrolizumab and in 84 (24%) patients treated with placebo plus pembrolizumab (appendix p 10). Treatment-related adverse events occurred in 280 (79%) of 353 patients in the epacadostat plus pembrolizumab group and 285 (81%) of 352 patients in the placebo plus pembrolizumab group (table 3). The most common treatment-related adverse events (any grade) were similar in both groups (table 3). Grade 3 or worse treatment-related adverse events occurred in 77 (22%) of 353 patients in the epacadostat plus pembrolizumab group and 60 (17%) of 352 patients in the placebo plus pembrolizumab group (appendix p 8–9). The most common grade 3 or worse treatment-related adverse event was lipase increase (14 [4%] of 353 patients receiving epacadostat plus pembrolizumab and 11 [3%] of 352 patients receiving placebo plus pembrolizumab; table 3), which was asymptomatic in all patients. 37 (10%) of 353 patients in the epacadostat plus pembrolizumab group and 32 (9%) of 352 patients in the placebo plus pembrolizumab group reported treatment-related serious adverse events. The most common grade 3 or worse treatment-related serious adverse events in the epacadostat plus pembrolizumab group were autoimmune hepatitis,

	Epacadostat plus pembrolizumab (n=353)			Placebo plus pembrolizumab (n=352)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Diarrhoea	37 (10%)	4 (1%)	0	43 (12%)	3 (1%)	0
Nausea	56 (16%)	1 (<1%)	0	37 (11%)	1 (<1%)	0
Asthenia	36 (10%)	0	0	31 (9%)	0	0
Fatigue	69 (20%)	2 (1%)	0	71 (20%)	0	0
Arthralgia	31 (9%)	1 (<1%)	0	36 (10%)	3 (1%)	0
Pruritus	61 (17%)	1 (<1%)	0	79 (22%)	0	0
Rash	49 (14%)	2 (1%)	0	56 (16%)	6 (2%)	0
Vitiligo	39 (11%)	0	0	39 (11%)	0	0
Increased lipase	12 (3%)	10 (3%)	4 (1%)	14 (4%)	7 (2%)	4 (1%)
Increased alanine aminotransferase	9 (3%)	8 (2%)	1 (<1%)	15 (4%)	1 (<1%)	0
Increased aspartate aminotransferase	13 (4%)	7 (2%)	0	19 (5%)	3 (1%)	0
Increased amylase	13 (4%)	2 (1%)	2 (1%)	18 (5%)	5 (1%)	0
Anaemia	4 (1%)	3 (1%)	0	6 (2%)	0	0
Autoimmune hepatitis	1 (<1%)	2 (1%)	1 (<1%)	0	1 (<1%)	0
Increased gamma-glutamyltransferase	1 (<1%)	2 (1%)	1 (<1%)	2 (1%)	1 (<1%)	0
Hepatitis	1 (<1%)	3 (1%)	0	0	0	0
Pneumonitis	4 (1%)	2 (1%)	1 (<1%)	7 (2%)	3 (1%)	0
Maculo-papular rash	13 (4%)	3 (1%)	0	16 (5%)	0	0
Abdominal pain	16 (5%)	2 (1%)	0	6 (2%)	0	0
Colitis	3 (1%)	2 (1%)	0	1 (<1%)	3 (1%)	1 (<1%)
Hypophosphataemia	3 (1%)	2 (1%)	0	0	0	0
Vomiting	15 (4%)	2 (1%)	0	11 (3%)	1 (<1%)	0
Acute kidney injury	0	0	1 (<1%)	2 (1%)	0	1 (<1%)
Adrenal insufficiency	0	1 (<1%)	0	3 (1%)	0	0
Anaphylactic reaction	0	1 (<1%)	0	0	0	0
Back pain	4 (1%)	1 (<1%)	0	2 (1%)	0	0
Increased blood creatine phosphokinase	1 (<1%)	1 (<1%)	0	1 (<1%)	0	0
Chronic inflammatory demyelinating polyradiculoneuropathy	0	1 (<1%)	0	0	0	0
Chronic obstructive pulmonary disease	0	1 (<1%)	0	0	0	0
Conjunctivitis	2 (1%)	1 (<1%)	0	0	0	0
Dermatitis exfoliative	0	1 (<1%)	0	0	0	0
Diabetic ketoacidosis	0	1 (<1%)	0	0	0	1 (<1%)
Dyspnoea	3 (1%)	1 (<1%)	0	12 (3%)	0	0
Electrocardiogram QT prolonged	1 (<1%)	1 (<1%)	0	0	1 (<1%)	0
Abnormal hepatic function	0	0	1 (<1%)	0	0	0
Hyperlipasaemia	0	1 (<1%)	0	0	0	2 (1%)
Hypertension	3 (1%)	1 (<1%)	0	4 (1%)	0	0
Hypoalbuminaemia	0	1 (<1%)	0	0	0	0
Hypophysitis	1 (<1%)	1 (<1%)	0	1 (<1%)	3 (1%)	0
Lung disorder	0	1 (<1%)	0	0	0	0
Myocarditis	0	1 (<1%)	0	0	0	0
Myositis	0	1 (<1%)	0	0	2 (1%)	0
Neck pain	3 (1%)	1 (<1%)	0	2 (1%)	0	0
Nephritis	3 (1%)	1 (<1%)	0	0	0	0
Neuralgia	0	1 (<1%)	0	1 (<1%)	0	0
Decreased neutrophil count	1 (<1%)	1 (<1%)	0	2 (1%)	0	0
Pancreatitis acute	0	1 (<1%)	0	0	0	1 (<1%)
Decreased platelet count	0	1 (<1%)	0	0	0	0
Pleural effusion	1 (<1%)	1 (<1%)	0	0	0	0
Scleroderma	0	1 (<1%)	0	0	0	0

(Table 3 continues on next page)

	Epacadostat plus pembrolizumab (n=353)			Placebo plus pembrolizumab (n=352)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Thrombocytopenia	1 (<1%)	0	1 (<1%)	0	0	0
Tumour flare	0	1 (<1%)	0	0	0	0
Arthritis	2 (1%)	0	0	2 (1%)	1 (<1%)	0
Increased bilirubin conjugated	0	0	0	0	1 (<1%)	0
Colitis ulcerative	0	0	0	0	1 (<1%)	0
Cytokine release syndrome	0	0	0	1 (<1%)	1 (<1%)	0
Deep vein thrombosis	0	0	0	0	1 (<1%)	0
Atopic dermatitis	0	0	0	0	1 (<1%)	0
Diabetes	0	0	0	1 (<1%)	1 (<1%)	0
Drug reaction with eosinophilia and systemic symptoms	0	0	0	0	1 (<1%)	1 (<1%)
Acute hepatitis	0	0	0	0	1 (<1%)	0
Hyperglycaemia	1 (<1%)	0	0	2 (1%)	2 (1%)	0
Hyponatraemia	0	0	0	1 (<1%)	0	1 (<1%)
Hypothyroidism	35 (10%)	0	0	31 (9%)	1 (<1%)	0
Infusion-related reaction	2 (1%)	0	0	3 (1%)	1 (<1%)	0
Lymphopenia	2 (1%)	0	0	4 (1%)	0	1 (<1%)
Malignant neoplasm progression	0	0	0	0	1 (<1%)	0
Decreased monocyte count	0	0	0	0	1 (<1%)	0
Mucosal inflammation	6 (2%)	0	0	1 (<1%)	1 (<1%)	0
Neutropenia	3 (1%)	0	0	0	0	1 (<1%)
Genital oedema	0	0	0	0	1 (<1%)	0
Pancreatitis	0	0	0	0	1 (<1%)	0
Polymyalgia rheumatica	0	0	0	0	1 (<1%)	0
Primary adrenal insufficiency	0	0	0	0	1 (<1%)	0
Pulmonary embolism	0	0	0	0	1 (<1%)	0
Increased troponin	0	0	0	0	1 (<1%)	0
Type 1 diabetes	0	0	0	1 (<1%)	0	1 (<1%)
Decreaed white blood cell count	0	0	0	2 (1%)	1 (<1%)	0

Data are n (%). Adverse events related to treatment with epacadostat or pembrolizumab. Treatment-related adverse events with grade 1 or grade 2 prevalence of 10% or worse in either treatment group and grade 3 or worse treatment-related adverse events reported in at least one patient in either group are listed. All grade 3 or worse treatment-related adverse events are reported in the appendix (pp 8–9). No deaths due to treatment-related adverse events were reported.

Table 3: **Treatment-related adverse events in the safety population**

diarrhoea, and pneumonitis (three [1%] of 353 each); the most common grade 3 or worse treatment-related serious adverse events in the placebo plus pembrolizumab group were colitis (four [1%] of 352), hypophysitis (three [1%]), and pneumonitis (three [1%]).

In the epacadostat plus pembrolizumab group, treatment-related adverse events led to treatment interruptions in 76 (22%) of 353 patients and treatment discontinuations in 39 (11%) patients (appendix pp 11–13). In the placebo plus pembrolizumab group, treatment-related adverse events led to treatment interruptions in 66 (19%) of 352 patients and treatment discontinuations in 34 (10%) patients (appendix pp 11–13). The most frequent adverse event leading to a discontinuation was increased alanine aminotransferase (nine [3%] of 353 patients in the epacadostat plus pembrolizumab group and two [<1%] of 352 in the placebo plus pembrolizumab group). In the epacadostat plus pembrolizumab group, 28 (8%) of 353 patients had a dose reduction of epacadostat from 100 mg to 50 mg and, of those, two (1%) patients had a dose reduction of epacadostat from 50 mg to 25 mg. In the placebo plus pembrolizumab group, 26 (7%) of 352 patients had a dose reduction of placebo from 100 mg to 50 mg and, of those, three (1%) patients had a dose reduction of placebo from 50 mg to 25 mg. In the epacadostat plus pembrolizumab group, there were seven deaths due to adverse events (death due to unknown cause [n=2], sepsis [n=2], peritonitis [n=1], pneumonia aspiration [n=1], and pulmonary embolism [n=1]). In the placebo plus pembrolizumab group, there were three deaths due to adverse events (sepsis [n=2] and septic shock [n=1]). No patient in either group died because of a treatment-related adverse event within 90 days after the last dose of study treatment.

Frequencies of adverse events of interest (adverse events with immune-related causes, regardless of

	Epacadostat plus pembrolizumab (n=353)			Placebo plus pembrolizumab (n=352)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Adrenal insufficiency						
Adrenal insufficiency	0	1 (<1%)	0	3 (1%)	0	0
Colitis						
Autoimmune colitis	0	0	0	2 (1%)	1 (<1%)	0
Colitis	4 (1%)	3 (1%)	0	1 (<1%)	4 (1%)	1 (<1%)
Guillain-Barre syndrome						
Axonal neuropathy	0	0	0	1 (<1%)	0	0
Hepatitis						
Autoimmune hepatitis	1 (<1%)	2 (1%)	1 (<1%)	0	1 (<1%)	0
Hepatitis	2 (1%)	3 (1%)	0	1 (<1%)	0	0
Acute hepatitis	0	0	0	0	1 (<1%)	0
Hyperthyroidism						
Hyperthyroidism	22 (6%)	0	0	25 (7%)	0	0
Hypophysitis						
Hypophysitis	1 (<1%)	1 (<1%)	0	1 (<1%)	3 (1%)	0
Hypopituitarism	0	0	0	1 (<1%)	0	0
Hypothyroidism						
Hypothyroidism	39 (11%)	0	0	32 (9%)	1 (<1%)	0
Infusion reactions						
Anaphylactic reaction	0	1 (<1%)	0	0	0	0
Cytokine release syndrome	0	0	0	1 (<1%)	1 (<1%)	0
Drug hypersensitivity	1 (<1%)	0	0	0	2 (1%)	0
Hypersensitivity	3 (1%)	0	0	3 (1%)	0	0
Infusion-related reaction	2 (1%)	0	0	3 (1%)	1 (<1%)	0
Myocarditis						
Myocarditis	0	1 (<1%)	0	0	0	0
Myositis						
Myopathy	1 (<1%)	0	0	0	0	0
Myositis	0	1 (<1%)	0	0	2 (1%)	0
Nephritis						
Autoimmune nephritis	0	0	0	2 (1%)	0	0
Nephritis	3 (1%)	1 (<1%)	0	0	0	0
Pancreatitis						
Pancreatitis	0	1 (<1%)	0	1 (<1%)	1 (<1%)	0
Acute pancreatitis	0	1 (<1%)	0	0	0	1 (<1%)
Pneumonitis						
Interstitial lung disease	1 (<1%)	0	0	1 (<1%)	0	0
Pneumonitis	4 (1%)	2 (1%)	1 (<1%)	7 (2%)	3 (1%)	0
Sarcoidosis						
Pulmonary sarcoidosis	1 (<1%)	0	0	0	0	0
Sarcoidosis	3 (1%)	0	0	0	0	0
Severe skin reactions						
Dermatitis exfoliative	0	1 (<1%)	0	0	0	0
Erythema multiforme	0	0	0	1 (<1%)	1 (<1%)	0
Pruritus	0	1 (<1%)	0	0	0	0
Rash	0	4 (1·1%)	0	0	7 (2%)	0
Maculo-papular rash	0	3 (1%)	0	0	1 (<1%)	0
Thyroiditis						
Autoimmune thyroiditis	2 (1%)	0	0	0	0	0
Thyroid disorder	0	0	0	1 (<1%)	0	0
Thyroiditis	8 (2%)	0	0	6 (2%)	0	0

(Table 4 continues on next page)

	Epacadostat plus pembrolizumab (n=353)			Placebo plus pembrolizumab (n=352)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
(Continued from previous page)						
Type 1 diabetes						
Diabetic ketoacidosis	0	1 (<1%)	0	0	0	1 (<1%)
Type 1 diabetes	0	0	0	1 (<1%)	0	1 (<1%)
Uveitis						
Uveitis	3 (1%)	0	0	1 (<1%)	0	0

Data are n (%). No deaths due to adverse events of interest were reported. *Adverse events on the basis of their probable immune cause and infusion reactions were based on a list of terms specified by the funder and were considered regardless of attribution to treatment or immune relatedness by the investigator (full listing of terms in the appendix, p 6).

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

attribution to study treatment) were similar across both treatment groups (table 4), except that hepatitis was more frequent in the epacadostat plus pembrolizumab group than in the placebo plus pembrolizumab group (table 4).

Discussion

In the phase 3 ECHO-301/KEYNOTE-252 study, the addition of epacadostat 100 mg twice daily to pembrolizumab did not result in greater clinical benefit compared with that of pembrolizumab monotherapy in patients with unresectable or metastatic melanoma previously untreated with a checkpoint inhibitor. We observed no differences in progression-free survival, overall survival, or objective response between the two study groups. Additionally, with the caveat that the study was not formally powered for subgroup analyses, no subgroup (prespecified or post hoc) had a clinically significant progression-free survival or overall survival benefit, including a retrospective testing of IDO1 expression comparing patients treated with epacadostat or placebo. On the basis of these results, the study was stopped as recommended by the independent, external data monitoring committee. Therefore, the interim analysis became the final analysis, with no additional efficacy assessment planned for this study. Safety data continue to be collected.

The absence of benefit of adding epacadostat 100 mg twice daily to pembrolizumab was surprising, given non-clinical and early-phase clinical data. For example, increased expression of IDO1 has been reported in multiple tumour types,[20] and IDO1 expression has been shown to correlate with prognosis in patients with melanoma.[8] In non-clinical studies, IDO1 expression prevented tumour rejection, RNA interference-mediated silencing of IDO1 hindered tumour growth,[20,21] and several IDO1 inhibitors—including epacadostat, navoximod, and indoximod—inhibited tumour growth.[22] In two open-label, phase 1–2 studies of patients with advanced melanoma, the combinations of epacadostat plus pembrolizumab (ECHO-202)[17] and epacadostat plus nivolumab (ECHO-204)[18] showed promising antitumour activity (56–65% of patients achieving an objective response) compared with historical data, at similar follow-up times as the phase 1–2 epacadostat studies, of the respective monotherapies for advanced melanoma (33% of patients with one or no systemic therapy for advanced disease achieved an objective response with pembrolizumab;[2] 40% of patients who were previously untreated achieved an objective response with nivolumab).[1] Epacadostat 100 mg twice daily was selected for this trial on the basis of a series of non-clinical and clinical observations that showed that the 100 mg twice daily dose achieved exposures in humans that had provided optimal activity in preclinical models, and that this dose was well tolerated in clinical studies.[16] Epacadostat doses with higher target coverage could be options for future investigations. Additionally, the importance of IDO1 expression as a target in melanoma remains controversial, because studies in the past decade in human melanoma tissue showed notable heterogeneity of IDO expression in longitudinal samples—ie, marked intra-patient and inter-patient variability[10]—similar to that seen with PD-L1 expression.[23] The high proportion of patients with an objective response and the favourable progression-free survival in two open-label, phase 1–2 trials of epacadostat in combination with PD-1 inhibition remains unexplained on the basis of patient demographics, tumour phenotypes, and other molecular features of the tumours studied in these trials. These include the proportions of patients with poor prognostic features, *BRAF*^{V600} mutations, and PD-L1 expression. Furthermore, these characteristics were similar to those in previously reported studies of pembrolizumab and nivolumab monotherapy in melanoma.[2,4,24]

Median progression-free survival for the placebo plus pembrolizumab group (4·9 months, 95% CI 2·9–6·8) in this phase 3 study was similar to that previously reported for pembrolizumab monotherapy in patients with advanced melanoma (4·1 months, 2·9–6·9),[2] whereas the median progression-free survival for the epacadostat plus pembrolizumab group (4·7 months, 2·9–6·8) in this phase 3 study was much lower than that reported for the same group in the phase 1–2 ECHO-202 study

(12·4 months).[17] A limitation of this study was that the design was based on early data for pembrolizumab monotherapy and a median progression-free survival of 4·75 months was assumed, potentially affecting statistical power assumptions. However, the 5-year survival outcomes from the KEYNOTE-001 study,[25] reported in 2018, showed a longer median progression-free survival of 8·3 months with pembrolizumab monotherapy in patients with advanced melanoma.

The encouraging median progression-free survival of patients in the phase 1–2 ECHO-202 report was probably not due to addition of epacadostat, but instead to the inclusion of a particularly favourable population either by chance or by uncontrolled positive selection due to the specific recruitment of participating centres or to a pre-existing opinion about the treatment. There were no major differences in eligibility criteria between the phase 1–2 ECHO-202 study and this phase 3 ECHO-301/KEYNOTE-252 study, and baseline demographics and disease characteristics were similar between the two studies. The only notable differences were the following: the phase 1–2 study was done solely in the USA, whereas the phase 3 study was done globally; and patients with previous *BRAF*^{V600} treatment were excluded from the treatment-naive cohort of the phase 1–2 study, but were eligible to enrol in the phase 3 study. Additionally, a difference in study design existed between studies: the phase 1–2 study used standard RECIST criteria (version 1.1) for selecting target lesions, whereas the phase 3 study used sponsor-modified RECIST criteria (version 1.1). The results of this study emphasise that prognostic and predictive markers of interest such as demographics, lactate dehydrogenase, *BRAF*^{V600} status, and PD-L1 status cannot adequately assess the prognosis for small groups of patients or for those treated with immunotherapy agents and, therefore, randomised phase 2 studies should be considered to further qualify promising new therapies for phase 3 assessment.

The combination of epacadostat 100 mg twice daily plus pembrolizumab was generally well tolerated on the basis of the reported adverse events, frequency of treatment interruptions and discontinuations, and overall safety profile, with minimal additive toxicity compared with that of pembrolizumab alone. Additionally, we observed no unexpected safety signals relative to previous reports of epacadostat[14] and pembrolizumab[2] monotherapies and to the phase 1–2 ECHO-202/KEYNOTE-037 study[16,17] of epacadostat plus pembrolizumab combination therapy. Regarding immune-related toxic effects, epacadostat plus pembrolizumab therapy seemed to be well tolerated compared with other immunotherapy combinations such as pembrolizumab plus low-dose ipilimumab[26] and nivolumab plus ipilimumab.[4,5] In this study, we observed similar frequencies of adverse events of interest between treatment groups, except for a higher frequency of hepatitis in the epacadostat plus pembrolizumab group compared with that in the placebo plus pembrolizumab group. Elevated liver enzymes have been previously reported as dose-limiting toxic effects in a phase 1–2 study[15] of epacadostat in combination with ipilimumab in patients with metastatic melanoma.

Our study had several limitations. There was little clinical information regarding the activity of IDO1 inhibitors in melanoma when the trial was designed, which might explain the negative results. IDO1 expression was not part of the eligibility criteria. Although potentially informative, analyses of some prespecified endpoints, including pharmacokinetics, anti-pembrolizumab antibodies, pharmacodynamics, and quality of life, were not done because no subgroups of interest based on clinical features or biomarkers were identified. Therefore, no rationale existed to devote further resources to the study, and the sponsors made the decision not to do the analyses for these endpoints. Finally, given the absence of predictive factors or biomarkers, it is not known how the results of this study might generalise to a different population.

In conclusion, the results of this phase 3 study indicate that the combination of epacadostat 100 mg twice daily and pembrolizumab 200 mg once every 3 weeks was generally well tolerated in patients with unresectable or metastatic melanoma, but showed no improvements in the proportion of patients achieving an objective response, in progression-free survival, or in overall survival compared with those of placebo plus pembrolizumab 200 mg once every 3 weeks. Overall, these results illustrate the challenge of proceeding to phase 3 assessment of a promising immunotherapy agent without evidence from a randomised phase 2 study. Future studies of epacadostat should incorporate dose and pharmacodynamic effects, as well as robust biomarker evaluations to improve the design of phase 3 studies. To further understand the results of this trial, additional analyses are ongoing and are expected to be reported in a separate paper once completed.

Contributors

GVL, RD, CR, JRA, JM, MJ, SJD, and TCM were involved in the design of the trial. GVL, RD, OH, TFG, CC, SD, MSC, J-JG, LD, CR, JL, JRA, and SJD obtained data and participated in the analysis and interpretation of the data. AA, TMK, JM, MJ, and TCM contributed to the analysis and interpretation of the data. All authors participated in the drafting and revising of the manuscript and approved the final version before submission.

Declaration of interests

GVL has served as a consultant or advisor for Amgen, Array, Bristol-Myers Squibb, Incyte, Merck Sharp and Dohme, Novartis, Pierre Fabre, and Roche; has received honoraria from Bristol-Myers Squibb, Incyte, Merck Sharp and Dohme, Novartis, and Roche; and personal fees for travel to conferences from Merck Sharp and Dohme and Roche. RD has served as a consultant or advisor for Amgen, Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, Pierre Fabre, Roche, Sanofi, Sun Pharma, and Takeda. OH has served as a consultant or advisor for Amgen, Bristol-Myers Squibb, Incyte, Merck, Novartis, and Roche, received honoraria from these companies, or both; served on speakers bureau for Amgen, Array, Bristol-Myers Squibb, Genentech, Novartis, and Sanofi; and his institution has received research funding from AstraZeneca, Bristol-Myers Squibb, Celldex, Genentech, Immunocore, Incyte, Merck, Merck Serono, Medimmune, Novartis, Pfizer, and Rinat. TFG has served on advisory boards for Merck and his institution has received research grants from Merck and Incyte.

CC has served as a consultant for AstraZeneca, Bayer, Bristol-Myers Squibb, and Merck Sharp and Dohme; served on speakers bureau for Bayer, Bristol-Myers Squibb, Eli Lilly, and Merck Sharp and Dohme; received personal fees and for travel and non-financial support from Boehringer Ingelheim and Bristol-Myers Squibb; and has received research grants from Astellas Pharma, AstraZeneca, Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, Medivation, Merck Sharp and Dohme, and Roche. SD received personal fees from Sanofi; non-financial support for travel and research from Bristol-Myers Squibb and Merck Sharp and Dohme; and research grant from Bristol-Myers Squibb. AA has served as a consultant and on speakers bureau for Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, and Roche. MSC has served as a consultant for Amgen, Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, and Pierre Fabre. J-JG has served as a consultant or advisor for Amgen, Bristol-Myers Squibb, Incyte, Merck/Pfizer, Merck Sharp and Dohme, Novartis, Pierre Fabre, Roche, Sanofi, and Sun Pharma, received honoraria from these companies, or both; has served on speakers bureau for Novartis; and received other support for travel from Amgen, Bristol-Myers Squibb, Merck Sharp and Dohme, Pierre Fabre, and Roche. TMK has received a research fund from AstraZeneca. LD has served as a consultant for and received honoraria and research grants from Bristol-Myers Squibb, Merck Sharp and Dohme, Novartis, and Roche. CR has served as a consultant or advisor for and received honoraria from Amgen, Bristol-Myers Squibb, Merck, Novartis, Pierre Fabre, and Roche. JL has served as a consultant for Achilles, AstraZeneca, Boston Biomedical, Bristol-Myers Squibb, Eisai, EUSA Pharma, GlaxoSmithKline, Ipsen, Imugene, Incyte, iOnctura, Kymab, Merck Serono, Merck Sharp and Dohme, Nektar Therapeutics, Novartis, Pierre Fabre, Pfizer, Roche/Genentech, Secarna, and Vitaccess; his institute has received grants from Achilles Therapeutics, Aveo, Bristol-Myers Squibb, Covance, Immunocore, Merck Sharp and Dohme, Nektar Therapeutics, Novartis, Pfizer, Pharmacyclics, and Roche; and has received non-financial support from the National Institute for Health Research RM/ICR Biomedical Research Centre for Cancer. JRA is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA. JM and MJ are employees and stockholders of Incyte. SJD is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA and stockholder of Merck & Co., Inc., Kenilworth, NJ, USA. TCM has served as a consultant or advisor for Bristol-Myers Squibb, Incyte, Merck, Aduro, and Novartis.

Data sharing

Access to individual patient-level data is not available for this study. The study protocol is available in the appendix (p 15).

Acknowledgments

This study was funded by Incyte Corporation (Wilmington, DE, USA) in collaboration with Merck Sharp & Dohme, a subsidiary of Merck (Kenilworth, NJ, USA). The authors wish to thank the patients and their families, the investigators, and the site personnel who participated in this study. Thank you to Jason Clark of Incyte Corporation and Ke Chen of Merck, for their statistical review of the manuscript. Medical writing assistance was provided by Andrew Gomes and Stella Chow, of CodonMedical, an Ashfield Company, part of UDG Healthcare, and was funded by Incyte Corporation. GVL was supported by an Australian NHMRC Practitioner Fellowship and the University of Sydney Medical Foundation. TFG is a recipient of a National Institutes of Health grant.

References

1 Robert C, Long GV, Brady B, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med* 2015; **372:** 320–30.

2 Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. *N Engl J Med* 2015; **372:** 2521–32.

3 Hodi FS, O'Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. *N Engl J Med* 2010; **363:** 711–23.

4 Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. *N Engl J Med* 2015; **373:** 23–34.

5 Hodi FS, Chiarion-Sileni V, Gonzalez R, et al. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018; **19:** 1480–92.

6 Munn DH, Mellor AL. Indoleamine 2,3-dioxygenase and tumor-induced tolerance. *J Clin Invest* 2007; **117:** 1147–54.

7 Okamoto A, Nikaido T, Ochiai K, et al. Indoleamine 2,3-dioxygenase serves as a marker of poor prognosis in gene expression profiles of serous ovarian cancer cells. *Clin Cancer Res* 2005; **11:** 6030–39.

8 Weinlich G, Murr C, Richardsen L, Winkler C, Fuchs D. Decreased serum tryptophan concentration predicts poor prognosis in malignant melanoma patients. *Dermatology* 2007; **214:** 8–14.

9 Krähenbühl L, Goldinger SM, Mangana J, et al. A longitudinal analysis of IDO and PDL1 expression during immune- or targeted therapy in advanced melanoma. *Neoplasia* 2018; **20:** 218–25.

10 Gide TN, Allanson BM, Menzies AM, et al. Inter- and intra-patient heterogeneity of indoleamine 2,3-dioxygenase expression in primary and metastatic melanoma cells and the tumor microenvironment. *Histopathology* 2019; **74:** 817–28.

11 Spranger S, Spaapen RM, Zha Y, et al. Up-regulation of PD-L1, IDO, and T(regs) in the melanoma tumor microenvironment is driven by CD8(+) T cells. *Sci Transl Med* 2013; **5:** 200ra116.

12 Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF. Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. *J Immunother Cancer* 2014; **2:** 3.

13 Koblish HK, Hansbury MJ, Bowman KJ, et al. Hydroxyamidine inhibitors of indoleamine-2,3-dioxygenase potently suppress systemic tryptophan catabolism and the growth of IDO-expressing tumors. *Mol Cancer Ther* 2010; **9:** 489–98.

14 Beatty GL, O'Dwyer PJ, Clark J, et al. First-in-human phase I study of the oral inhibitor of indoleamine 2,3-dioxygenase-1 epacadostat (INCB024360) in patients with advanced solid malignancies. *Clin Cancer Res* 2017; **23:** 3269–76.

15 Gibney GT, Hamid O, Lutzky J, et al. Updated results from the phase 1/2 study of epacadostat (INCB024360) in combination with ipilimumab in patients with metastatic melanoma. 18th European Cancer Organisation—40th ESMO European Cancer Congress; Vienna, Austria; Sept 25–29, 2015.

16 Mitchell TC, Hamid O, Smith DC, et al. Epacadostat plus pembrolizumab in patients with advanced solid tumors: phase I results from a multicenter, open-label phase I/II trial (ECHO-202/KEYNOTE-037). *J Clin Oncol* 2018; **36:** 3223–3230.

17 Hamid O, Gajewski T, Frankel A, et al. Epacadostat plus pembrolizumab in patients with advanced melanoma: phase 1 and 2 efficacy and safety results from ECHO-202/KEYNOTE-037. *Ann Oncol* 2017; **28** (suppl 5)**:** 428–48.

18 Daud A, Saleh MN, Hu J, et al. Epacadostat plus nivolumab for advanced melanoma: updated phase 2 results of the ECHO-204 study. *J Clin Oncol* 2018; **36** (suppl 15)**:** 9511.

19 Pratta MA. RNAscope as a platform to detect IDO1 expression in tumor tissue sections. *J Clin Oncol* 2018; **36** (suppl 5)**:** 116.

20 Uyttenhove C, Pilotte L, Theate I, et al. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med* 2003; **9:** 1269–74.

21 Zheng X, Koropatnick J, Li M, et al. Reinstalling antitumor immunity by inhibiting tumor-derived immunosuppressive molecule IDO through RNA interference. *J Immunol* 2006; **177:** 5639–46.

22 Prendergast GC, Malachowski WJ, Mondal A, Scherle P, Muller AJ. Indoleamine 2,3-dioxygenase and its therapeutic inhibition in cancer. *Int Rev Cell Mol Biol* 2018; **336:** 175–203.

23 Madore J, Vilain RE, Menzies AM, et al. PD-L1 expression in melanoma shows marked heterogeneity within and between patients: implications for anti-PD-1/PD-L1 clinical trials. *Pigment Cell Melanoma Res* 2015; **28:** 245–53.

24 Hamid O, Robert C, Daud A, et al. Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. *N Engl J Med* 2013; **369:** 134–44.

25 Hamid O, Robert C, Daud A, et al. 5-year survival outcomes in patients (pts) with advanced melanoma treated with pembrolizumab (pembro) in KEYNOTE-001. *J Clin Oncol* 2018; **36** (suppl 15)**:** 9516.

26 Long GV, Atkinson V, Cebon JS, et al. Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial. *Lancet Oncol* 2017; **18:** 1202–10.