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Standard-dose pembrolizumab in combination with reduced-dose ipilimumab for patients with advanced melanoma (KEYNOTE-029): an open-label, phase 1b trial

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Summary

Background Reduced-dose nivolumab in combination with standard-dose ipilimumab improves objective response and progression-free survival compared with standard-dose ipilimumab alone, but increases toxicity. We assessed the safety and anti-tumour activity of standard-dose pembrolizumab in combination with reduced-dose ipilimumab.

Methods In this open-label, phase 1b trial, we recruited patients from 12 medical centres in Australia, New Zealand, and the USA. Eligible patients were aged at least 18 years, had advanced melanoma, had an Eastern Cooperative Oncology Group performance status of 0 or 1, had measurable disease according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, had adequate organ function, had resolution of toxic effects of the most recent previous chemotherapy to grade 1 or less, had no active autoimmune disease requiring systemic steroids or immunosuppressive agents, had no active non-infectious pneumonitis, had no uncontrolled thyroid dysfunction or diabetes, had no active brain metastases, and had not received previous immune checkpoint inhibitor therapy. Patients received intravenous pembrolizumab 2 mg/kg plus intravenous ipilimumab 1 mg/kg every 3 weeks for four doses, followed by intravenous pembrolizumab 2 mg/kg every 3 weeks for up to 2 years or disease progression, intolerable toxicity, withdrawal of consent, or investigator decision. The primary endpoint was safety and tolerability. The proportion of patients achieving an objective response assessed per RECIST version 1.1 by independent central review and overall survival were secondary endpoints. We also assessed progression-free survival. The primary endpoint was assessed in all patients who received at least one dose of combination therapy. Activity was assessed in all enrolled patients. This trial is registered with ClinicalTrials.gov, number NCT02089685. Enrolment into this cohort is closed, but patients are still being monitored for safety and anti-tumour activity.

Findings Between Jan 13, 2015, and Sept 17, 2015, we enrolled and treated 153 patients. As of the Oct 17, 2016, cutoff date, median follow-up was 17·0 months (IQR 14·8–18·8). 110 (72%) of 153 patients received all four pembrolizumab plus ipilimumab doses; 64 (42%) remained on pembrolizumab monotherapy. 110 grade 3–4 treatment-related adverse events occurred in 69 (45%) patients. No treatment-related deaths occurred. Treatment-related adverse events led to discontinuation of pembrolizumab and ipilimumab in 22 (14%) patients, including 17 (11%) who discontinued both treatments for the same event and five (3%) who discontinued ipilimumab for one event and later discontinued pembrolizumab for another. 12 (8%) patients discontinued ipilimumab only and 14 (9%) discontinued pembrolizumab only because of treatment-related adverse events. 158 immune-mediated adverse events of any grade occurred in 92 (60%) patients, and 50 immune-mediated adverse events of grade 3–4 occurred in 42 (27%) patients; the most common immune-mediated adverse events were hypothyroidism (25 [16%]) and hyperthyroidism (17 [11%]). 93 (61% [95% CI 53–69]) patients achieved an objective response. Estimated 1 year progression-free survival was 69% (95% CI 60–75), and estimated 1 year overall survival was 89% (95% CI 83–93).

Interpretation Standard-dose pembrolizumab given in combination with four doses of reduced-dose ipilimumab followed by standard-dose pembrolizumab has a manageable toxicity profile and provides robust anti-tumour activity in patients with advanced melanoma. These data suggest that standard-dose pembrolizumab plus reduced-dose ipilimumab might be a tolerable, efficacious treatment option for patients with advanced melanoma. A randomised phase 2 trial of alternative dosing strategies of this combination is underway.

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Introduction

Immune checkpoint blockade has become a standard of care for the treatment of advanced melanoma. The cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab was the first immune checkpoint inhibitor to show a survival benefit in patients with advanced melanoma.[1,2] Subsequently, the programmed death 1 (PD-1) inhibitors pembrolizumab[3–7] and nivolumab[8–11] have shown efficacy in previously untreated and ipilimumab-treated advanced melanoma. In the phase 3 KEYNOTE-006 trial,[6,12]

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Research in context

Evidence before this study

We searched PubMed on March 15, 2017, using the individual search terms "PD-1" OR "programmed death 1", "PD-L1" OR "programmed death ligand 1", "pembrolizumab" OR "MK-3475" OR "lambrolizumab" OR "keytruda", "nivolumab" OR "BMS-936558" OR "opdivo", "ipilimumab" OR "yervoy", "atezolizumab" OR "MPDL3280A", "durvalumab" OR "MEDI4736", and "avelumab" OR "MSB0010718C". We also did the following combination searches: "nivolumab" AND "ipilimumab" AND "combination", "pembrolizumab" AND "ipilimumab" AND "combination", "PD-1" AND "CTLA-4" AND "combination", and "PD-L1" AND "CTLA-4" AND "combination". We combined all searches with "melanoma" and did not limit them by date, but limited them to the English language. We identified three published clinical trials of nivolumab plus ipilimumab for advanced melanoma: a phase 1 dose-finding trial, the randomised controlled phase 2 CheckMate 069 study, and the randomised controlled phase 3 CheckMate 067 study.

Added value of this study

Data from this study show that combination therapy with standard-dose pembrolizumab and reduced-dose ipilimumab is tolerable and has substantial anti-tumour activity in patients with advanced melanoma. These data suggest that treatment with a standard dose of anti-programmed death 1 therapy and a reduced dose of anti-cytotoxic T-lymphocyte-associated protein 4 therapy is feasible and warrants further exploration.

Implications of all the available evidence

In this large phase 1 trial, the toxicity profile and anti-tumour activity of standard-dose pembrolizumab plus reduced-dose ipilimumab compared favourably with those observed in the phase 3 trial of reduced-dose nivolumab plus standard-dose ipilimumab. These data support use of anti-programmed death 1 and anti-cytotoxic T-lymphocyte-associated protein 4 combination therapy in patients with advanced melanoma and suggest that combination of standard-dose pembrolizumab and reduced-dose ipilimumab might be a viable treatment option for these patients.

pembrolizumab 10 mg/kg given every 2 weeks or every 3 weeks showed significantly better overall survival, progression-free survival, and objective response than did ipilimumab in patients with advanced melanoma, as well as a lower proportion of grade 3–5 treatment-related adverse events despite the longer treatment exposure of pembrolizumab than of ipilimumab.

CTLA-4 and PD-1 are inhibitory receptors that suppress anti-tumour immune activity at different stages: CTLA-4 interferes with T-cell activation at antigen presentation during the priming phase, whereas PD-1 downregulates T-cell activity at the tumour site during the effector phase.[13] These non-redundant, complementary mechanisms of action led to synergistic anti-tumour activity of combined CTLA-4 and PD-1 inhibition in preclinical models.[14,15] Clinically, combination of PD-1 and CTLA-4 inhibition has shown efficacy in several clinical trials.[8,16,17] In the phase 3 CheckMate 067 trial,[8,18] combination of reduced-dose nivolumab with standard-dose ipilimumab for four doses followed by standard-dose nivolumab alone improved overall survival, progression-free survival, and objective response compared with standard-dose ipilimumab. However, the significant improvement in efficacy was accompanied by increased toxicity, including a high proportion of grade 3–4 treatment-related adverse events, with an associated increase in treatment discontinuation. These findings raised the question of whether or not standard-dose anti-PD-1 combined with reduced-dose ipilimumab could show substantial clinical activity while avoiding severe toxicity.

In the KEYNOTE-029 trial, we assessed the safety and anti-tumour activity of standard-dose pembrolizumab given in combination with reduced-dose ipilimumab in patients with advanced melanoma. In an initial safety run-in that enrolled 22 patients with advanced melanoma or renal cell carcinoma, this combination showed an acceptable safety profile and preliminary evidence of anti-tumour activity.[19] In this study, we present results from the KEYNOTE-029 expansion cohort of patients with advanced melanoma receiving standard-dose pembrolizumab plus reduced-dose ipilimumab.

See Online for appendix

Methods

Study design and participants

In this open-label, phase 1b trial, we recruited patients from 12 medical centres in Australia, New Zealand, and the USA into the expansion cohort (appendix p 2). Eligible patients were aged at least 18 years and had histologically confirmed, unresectable stage III or IV melanoma, excluding uveal melanoma; an Eastern Cooperative Oncology Group performance status of 0 or 1; measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1;[20] adequate organ function; resolution of toxic effects of the most recent previous chemotherapy to grade 1 or less (except alopecia); no previous therapy with an anti-PD-1, anti-programmed death ligand 1 (PD-L1), anti-programmed death ligand 2, anti-CD137, or anti-CTLA-4 antibody; no active autoimmune disease requiring systemic steroids or immunosuppressive agents; no active non-infectious pneumonitis; and no uncontrolled thyroid dysfunction or diabetes. We excluded patients with active brain or leptomeningeal metastases; patients with previously treated, stable brain metastases were eligible. All patients were required to provide an adequate archival or newly collected melanoma tissue sample for PD-L1

immunohistochemistry. Full inclusion and exclusion criteria are listed in the appendix (pp 3–4).

The study protocol and associated amendments were approved by the appropriate institutional review boards and ethics committees at each centre. We did the study in accordance with the protocol and subsequent amendments, Good Clinical Practice Guidelines, and the Declaration of Helsinki. All patients provided written informed consent.

Procedures

Patients received pembrolizumab 2 mg/kg intravenously for 30 min once every 3 weeks followed by ipilimumab 1 mg/kg intravenously for 90 min once every 3 weeks for four doses, followed by pembrolizumab 2 mg/kg intravenously for 30 min every 3 weeks for up to 2 years. We continued treatment until disease progression, intolerable toxicity, withdrawal of consent, or investigator decision. If an investigator considered an adverse event to be caused by ipilimumab, patients could discontinue ipilimumab and continue pembrolizumab on resolution of the event to grade 0 or 1; if pembrolizumab was discontinued, ipilimumab was discontinued as well. Patients with radiological disease progression who were clinically stable could continue treatment until a scan was done a minimum of 4 weeks later. If progression was confirmed but the patient was clinically stable and considered to be deriving clinical benefit, treatment could be continued. Patients who achieved complete response could discontinue pembrolizumab if they received treatment for at least 24 weeks, maintained complete response for at least two scans after complete response was declared, and received at least two pembrolizumab doses after complete response was confirmed. For full criteria for removal of a patient from the study, and for details of permitted treatment reductions and interruptions, see appendix (pp 64–68). Pembrolizumab dose reductions were not permitted. The ipilimumab dose could be reduced to 0·3 mg/kg after the first occurrence of a grade 3–4 haematological toxicity or grade 3 non-haematological toxicity that resolved within 4 weeks or after the first occurrence of a grade 1–2 non-haematological toxicity that did not resolve within 4 weeks; ipilimumab was to be discontinued on recurrence.

PD-L1 expression in tumour samples was assessed during the screening period at a central laboratory using an immunohistochemistry assay (Agilent Technologies, Carpinteria, CA, USA) and the 22C3 antibody (Merck & Co, Inc, Kenilworth, NJ, USA). We defined positivity as staining on at least 1% of tumour cells or mononuclear inflammatory cells intercalated within or contiguous to tumour nests. We did tumour imaging at baseline and week 12 and then every 6 weeks until week 30 and every 12 weeks thereafter. Response was assessed according to RECIST version 1.1[20] by independent central review for formal assessment of anti-tumour activity and according to modified RECIST by investigator review for informing treatment decisions. We assessed adverse events, laboratory values, and vital signs regularly throughout the study and graded adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[21]

Outcomes

The primary objective was to assess the safety and tolerability of pembrolizumab plus ipilimumab on the basis of the prevalence of adverse events, including adverse events of special interest based on an immunological mechanism of action (ie, immune-mediated). We derived immune-mediated adverse events from a list of terms specified by the funder (appendix p 6) and included them as immune-mediated events regardless of whether they were considered to be immune related or treatment related by the investigator. Secondary endpoints were the proportion of patients with an objective response (defined as complete or partial response according to RECIST version 1.1[20]), duration of response (defined as the time from first evidence of response until disease progression or death), overall survival (defined as the time from enrolment to death from any cause), ordinal response score, and relation between PD-L1 expression according to immunohistochemistry and objective response, progression-free survival, and overall survival. Progression-free survival (defined as the time from enrolment to radiologically confirmed disease progression or death from any cause) was also assessed in the total population, but was not a prespecified outcome.

Statistical analysis

The results reported in this study are based on an analysis done after all patients had at least 12 months of follow-up. Up to 150 patients were to be enrolled, with a goal of approximately 25% of patients with PD-L1-negative tumours being enrolled to assess the proportion of patients with an objective response in this subgroup. With 22 patients with PD-L1-negative tumours enrolled, the study had 80% power to rule out a lower bound of the proportion of these patients with an objective response of 15% if the true proportion was 40%. We assessed safety (primary outcome) in all patients who received at least one dose of combination therapy. We assessed objective response and overall survival (secondary outcomes) in all enrolled patients. We also assessed progression-free survival in all enrolled patients. We assessed the duration of response (secondary outcome) in all patients who had complete or partial response. We provided descriptive statistics for baseline characteristics, patient disposition, and adverse events. We used the Kaplan-Meier method to estimate progression-free survival, overall survival, and duration of response. We calculated the event rate per 100 person-years of exposure for immune-mediated adverse events as (number of events×100)/person-years of exposure, in which exposure is defined as minimum (last dose date+30 or data cutoff date)−first dose date+1. We did statistical analyses using SAS version 9.3. This trial is

	Pembrolizumab plus ipilimumab (n=153)
Age (years)	60 (53–70)
Sex	
Men	101 (66%)
Women	52 (34%)
ECOG performance status	
0	113 (74%)
1	40 (26%)
Lactate dehydrogenase concentration	
Normal	114 (75%)
>ULN	38 (25%)
Missing	1 (1%)
PD-L1 status*	
Positive	127 (83%)
Negative	24 (16%)
Nonassessable or indeterminate	2 (1%)
BRAF^{V600} mutation	
Present	55 (36%)
Absent	90 (59%)
Unknown	8 (5%)
M stage	
M0	5 (3%)†
M1a	20 (13%)
M1b	43 (28%)
M1c	85 (56%)
Lines of previous systemic therapy for advanced disease	
None	133 (87%)
One	18 (12%)
Two	2 (1%)
Previous BRAF inhibitor with or without MEK inhibitor	15 (10%)
Previous chemotherapy	2 (1%)

Data are median (IQR) or n (%). ECOG=Eastern Cooperative Oncology Group. ULN=upper limit of normal. PD-L1=programmed death ligand 1. BRAF=B-Raf proto-oncogene, serine/threonine kinase. M=metastasis. *PD-L1 positivity was defined as staining on at least 1% of tumour cells or mononuclear inflammatory cells intercalated within or contiguous to tumour nests. †All five patients had stage IIIC disease.

Table 1: **Baseline characteristics**

registered with ClinicalTrials.gov, number NCT02089685. Enrolment into this cohort is closed, but patients are still being monitored for safety and anti-tumour activity. The originally planned phase 2 part of the trial was not pursued in light of the results of the phase 1 pembrolizumab plus pegylated interferon alfa-2b dose-finding cohort.[22]

Role of the funding source

Representatives of the funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The funder maintained the study database. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 13, 2015, and Sept 17, 2015, we enrolled 153 patients, all of whom received at least one dose of pembrolizumab plus ipilimumab (appendix p 5) and thus were evaluable for safety and efficacy. Most patients were previously untreated and had PD-L1-positive tumours, normal serum lactate dehydrogenase concentrations, and an Eastern Cooperative Oncology Group performance status of 0 (table 1). 55 (36%) of 153 patients had *BRAF*^{V600}-mutant tumours, including 13 (8%) who received previous BRAF inhibitor therapy with or without MEK inhibitor therapy.

As of the Oct 17, 2016, cutoff date, all 153 patients had at least 12 months of follow-up (median 17·0 months [IQR 14·8–18·8]) and 64 (42%) remained on pembrolizumab monotherapy. The most common reasons for discontinuation of treatment were adverse events (40 [26%] of 153) and clinical or radiological disease progression (35 [23%]); eight (5%) discontinued pembrolizumab after achieving complete response (appendix p 5). 110 (72%) of 153 patients received all four doses of combined pembrolizumab and ipilimumab, 22 (14%) received three, 11 (7%) received two, and ten (7%) received one.

147 (96%) of 153 patients had at least one treatment-related adverse event, including 69 (45%) who had at least one adverse event of grade 3–4 severity (table 2). No treatment-related deaths occurred. Four (3%) patients died because of non-treatment-releated adverse events: three (2%) because of disease progression and one (1%) because of acute coronary syndrome. Treatment-related adverse events led to discontinuation of ipilimumab only in 12 (8%) patients and pembrolizumab only in 14 (9%) patients. An additional 22 (14%) patients discontinued both ipilimumab and pembrolizumab for treatment-related adverse events, including 17 (11%) who discontinued both treatments for the same adverse event and five (3%) who discontinued ipilimumab for one event and later discontinued pembrolizumab for another. 13 (27%) of the 48 patients who discontinued treatment because of treatment-related adverse events did so because of laboratory abnormalities. Four (3%) of 153 patients had their ipilimumab dose reduced because of treatment-related adverse events: three (2%) because of increased lipase concentration and one (1%) because of autoimmune hepatitis. During pembrolizumab monotherapy, 44 (29%) patients interrupted therapy because of treatment-related adverse events. The most common treatment-related adverse events of any grade were fatigue (74 [48%]), rash (64 [42%]), and pruritus (63 [41%]; table 2). Grade 3–4 treatment-related events that occurred in five or more patients were elevated lipase concentration (25 [16%]), autoimmune hepatitis (nine [6%]), colitis (eight [5%]), and elevated amylase concentration (six [4%]; table 2, appendix pp 7–10); four (67%) of the six patients with grade 3–4 treatment-related elevated amylase concentration also had elevated lipase concentration. 769 (67%) of the

	Grade 1–2	Grade 3	Grade 4
Any	78 (51%)	59 (39%)	10 (7%)
Fatigue	74 (48%)	0	0
Rash	60 (39%)	4 (3%)	0
Pruritus	63 (41%)	0	0
Diarrhoea	39 (25%)	1 (1%)	0
Lipase concentration increased	7 (5%)	17 (11%)	8 (5%)
Vitiligo	30 (20%)	0	0
Nausea	26 (17%)	0	0
Amylase concentration increased	19 (12%)	5 (3%)	1 (1%)
Dry mouth	25 (16%)	0	0
Hypothyroidism	24 (16%)	0	0
Arthralgia	19 (12%)	1 (1%)	0
Maculopapular rash	18 (12%)	1 (1%)	0
Alanine aminotransferase concentration increased	15 (10%)	3 (2%)	0
Aspartate aminotransferase concentration increased	17 (11%)	0	0
Hyperthyroidism	14 (9%)	2 (1%)	0
Headache	15 (10%)	1 (1%)	0
Pneumonitis	13 (8%)	3 (2%)	0
Autoimmune hepatitis	6 (4%)	9 (6%)	0
Hypophysitis	12 (8%)	2 (1%)	0
Colitis	3 (2%)	8 (5%)	0
γ-glutamyltransferase concentration increased	9 (6%)	2 (1%)	0
Pruritic rash	7 (5%)	2 (1%)	0
Macular rash	6 (4%)	1 (1%)	0
Drug eruption	4 (3%)	2 (1%)	0
Blood creatine phosphokinase concentration increased	3 (2%)	1 (1%)	0
Autoimmune colitis	0	3 (2%)	0
Type 1 diabetes	0	2 (1%)	1 (1%)
Autoimmune pancreatitis	1 (1%)	1 (1%)	0
Musculoskeletal pain	1 (1%)	1 (1%)	0
Tubulointerstitial nephritis	1 (1%)	1 (1%)	0
Vertigo	1 (1%)	1 (1%)	0
Acute adrenocortical insufficiency	0	1 (1%)	0
Angioedema	0	1 (1%)	0
Blood cortisol concentration increased	0	1 (1%)	0
Cytokine release syndrome	0	1 (1%)	0
Deafness	0	1 (1%)	0

(Table 2 continues in next column)

	Grade 1–2	Grade 3	Grade 4
(Continued from previous column)			
Diabetes	0	1 (1%)	0
Diabetic ketoacidosis	0	0	1 (1%)
Diverticulitis	0	1 (1%)	0
Drug reaction with eosinophilia and systemic symptoms	0	1 (1%)	0
Enteritis	0	1 (1%)	0
Glomerulonephritis	0	1 (1%)	0
Hepatic enzyme concentration increased	0	1 (1%)	0
Hypertension	0	1 (1%)	0
Lymphocytic hypophysitis	0	1 (1%)	0
Aseptic meningitis	0	1 (1%)	0
CNS metastases	0	1 (1%)	0
Mycoplasma infection	0	1 (1%)	0
Pemphigoid	0	1 (1%)	0
Viral infection	0	1 (1%)	0

Data are n (%) and listed in order of descending total prevalence. n=153. Relationship to study treatment was established by the investigator. We included grade 1–2 events if they occurred in at least 10% of patients. All grade 3–4 events are included.

Table 2: **Treatment-related adverse events**

	Grade 1–2	Grade 3	Grade 4
Hypothyroidism	25 (16%)	0	0
Hyperthyroidism	15 (10%)	2 (1%)	0
Hypophysitis	13 (8%)	3 (2%)	0
Pneumonitis	13 (8%)	3 (2%)	0
Hepatitis	6 (4%)	9 (6%)	0
Colitis	3 (2%)	11 (7%)	0
Skin reactions	1 (1%)	12 (8%)	0
Thyroiditis	8 (5%)	0	0
Infusion reactions	5 (3%)	1 (1%)	0
Adrenal insufficiency	4 (3%)	1 (1%)	0
Pancreatitis	4 (3%)	1 (1%)	0
Uveitis	4 (3%)	0	0
Nephritis	1 (1%)	2 (1%)	0
Type 1 diabetes	0	2 (1%)	1 (1%)
Myositis	1 (1%)	0	0

Data are n (%) and in order of descending total prevalence. n=153.

Table 3: **Immune-mediated adverse events**

1155 any-grade and 87 (79%) of the 110 grade 3–4 treatment-related adverse events had resolved by data cutoff.

158 immune-mediated adverse events of any grade occurred in 92 (60%) of 153 patients; 42 (27%) had grade 3–4 adverse events (table 3). Including recurrences, 61 (40%) patients reported no immune-mediated events, 45 (29%) reported one event, 32 (21%) reported two events, 11 (7%) reported three events, and four (3%) reported four events. Immune-mediated adverse events led to discontinuation of ipilimumab only in 11 (7%) patients, both ipilimumab and pembrolizumab in 14 (9%), and pembrolizumab only in eight (5%). The most common immune-mediated events were endocrinopathies, including hypothyroidism (25 [16%]), hyperthyroidism (17 [11%]), and hypophysitis (16 [10%]; table 3). Other common immune-mediated events were pneumonitis (16 [10%]), hepatitis (15 [10%]), colitis (14 [9%]), and skin

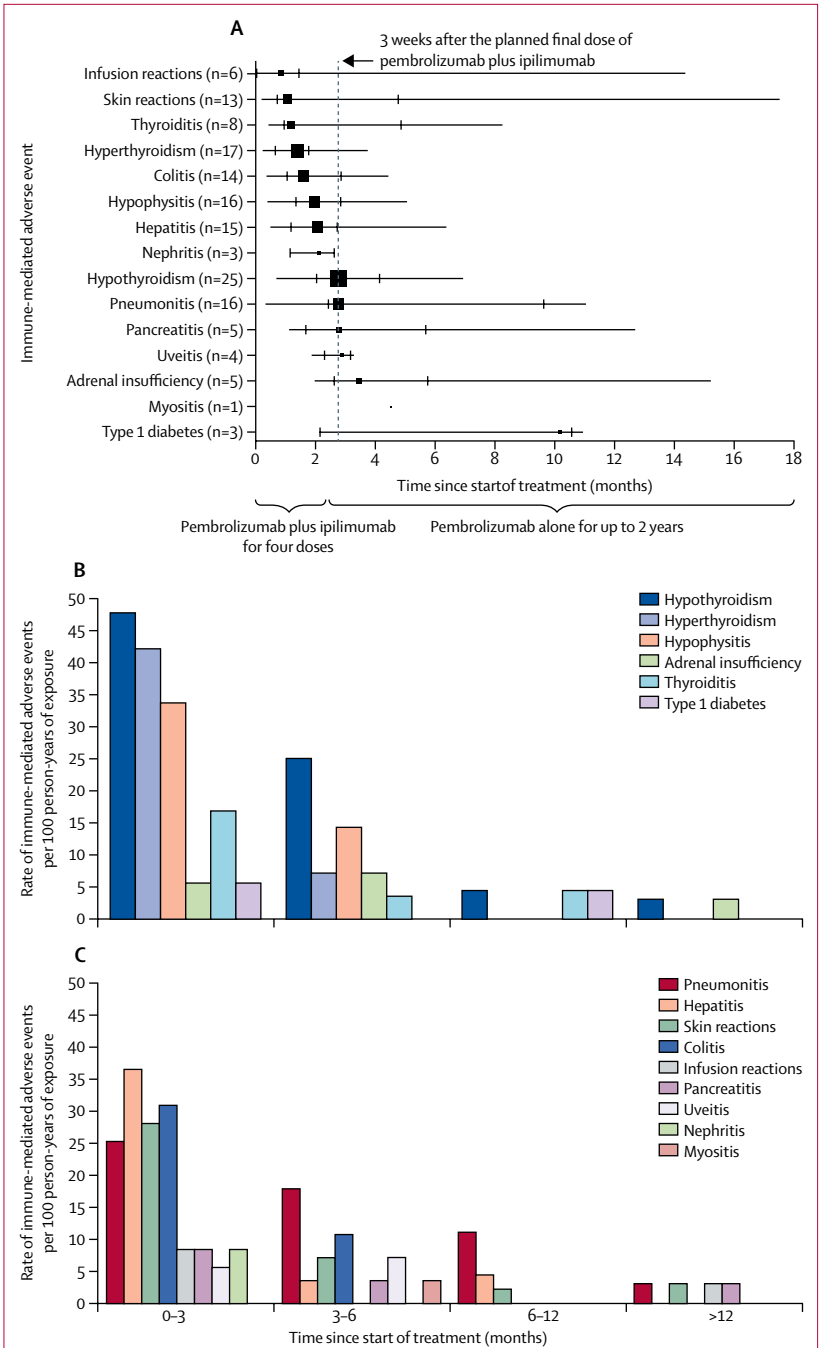

Figure 1: **Kinetics of immune-mediated adverse events**
(A) Time to onset. Median is represented by the square, the lower and upper quartiles are represented by vertical lines, and the range is represented by the length of the bar. The size of the squares represent the relative population size. Exposure-adjusted incidence of (B) endocrinopathies and (C) events that were not endocrinopathies by time since the start of study treatment.

reactions (13 [8%]). The only grade 3–4 immune-mediated events with a prevalence of 5% or greater were skin reactions, colitis, and hepatitis. We used systemic corticosteroids to manage 90 (57%) of 158 immune-mediated events, including all episodes of adrenal insufficiency, colitis, hepatitis, hypophysitis, and nephritis (appendix p 11). We used infliximab to manage eight (5%) of 158 events (all colitis), mycophenolate mofetil to manage three (2%) events (two [1%] hepatitis and one [1%] nephritis), and sulfasalazine to manage one (1%) event (colitis).

Median time to onset of immune-mediated adverse events that occurred in more than one patient ranged from 26 days to 310 days (figure 1). Exposure-adjusted event rates were highest in the first 3 months of treatment for all immune-mediated adverse events except for the low-frequency events (adrenal insufficiency, myositis, and uveitis), for which the event rates were highest from 3 months to 6 months after starting treatment (figure 1). At data cutoff, 88 (56%) of the 158 immune-mediated events had resolved, including 37 (74%) of 50 grade 3–4 events (appendix p 11). Excluding endocrinopathies, 65 (80%) of 81 immune-mediated events of any grade resolved and 33 (83%) of 40 grade 3–4 events resolved. Considering individual events, hypophysitis, adrenal insufficiency, and hypothyroidism were the least frequently resolved, whereas all cases of hepatitis, pancreatitis, and uveitis resolved by data cutoff.

After a median follow-up of 17·0 months, 93 (61% [95% CI 53–69]) of 153 patients had an objective response (table 4). 114 (82%) of 139 assessable patients had a decrease from baseline in tumour size, and the median change from baseline was –63% (figure 2). The proportion of patients with an objective response was similar in patients with PD-L1-positive and PD-L1-negative tumours (table 4). The proportion of patients with an objective response was also similar in other subgroups examined, including previous treatment, baseline lactate dehydrogenase concentration, and *BRAF* mutation, with overlapping 95% CIs (appendix p 12). 34 (63% [95% CI 49–76]) of 54 patients who discontinued pembrolizumab or ipilimumab because of an adverse event, regardless of attribution to treatment, had an objective response. When considering the proportion of patients who achieved an objective response by the number of ipilimumab doses, it was lowest in patients who received one dose (two [20% (95% CI 2–56)] of ten), similar in those who received two (five [45% (17–77)] of 11) and three (13 [59% (36–79)] of 22) doses, and highest in those who received all four (73 [66% (57–75)] of 110) doses; however, subgroups are small, and 95% CIs overlap. Kaplan-Meier analysis of progression-free survival is shown in figure 2 and table 4. Estimated 1 year progression-free survival was 69% (95% CI 60–75; table 4). 18 (12%) of 153 patients died. Median overall survival was not reached (95% CI not estimable to not estimable); the estimated proportion of patients alive at 12 months was 89% (95% CI 83–93; figure 2). Overall survival according to PD-L1 expression is not presented because the number of deaths that have accrued is not sufficient to do a meaningful subgroup analysis. Ordinal response score results are being analysed and might be presented elsewhere on completion.

Discussion

In this expansion cohort of a phase 1b trial, we show that combination of standard-dose pembrolizumab with reduced-dose ipilimumab had a manageable toxicity profile and substantial anti-tumour activity.

At the time that this study was done, pembrolizumab 2 mg/kg every 3 weeks was the standard dose of pembrolizumab approved by the US Food and Drug Administration and European Medicines Agency on the basis of the results of pharmacokinetic analyses[23] and randomised dose comparisons showing similar efficacy and safety for both 2 mg/kg and 10 mg/kg every 3 weeks[4,7] and 10 mg/kg both every 2 weeks and 3 weeks.[6,7] The combination of standard-dose pembrolizumab with reduced-dose ipilimumab explored in this study was associated with higher toxicity than that reported for pembrolizumab or ipilimumab monotherapy.[1,4,6–8,17] Hypothyroidism was more frequent with the combination than with pembrolizumab monotherapy (16% *vs* 5–10%), as were hyperthyroidism (11% *vs* 2–5%), and pneumonitis (10% *vs* 1–3%).[4,6,7] Toxicities typically associated with ipilimumab were also more frequent with the combination than were those reported for ipilimumab monotherapy, including hepatitis (10% *vs* 1–4%) and hypophysitis (10% *vs* 2%).[1,6,8,17]

By contrast, the toxicity profile of standard-dose pembrolizumab plus reduced-dose ipilimumab compared favourably with that of reduced-dose nivolumab combined with standard-dose ipilimumab. Some ipilimumab-associated toxicities appear to be more frequent with the nivolumab plus ipilimumab combination (eg, colitis [12%] and diarrhoea [44%]) than with the pembrolizumab plus ipilimumab combination (colitis [9%] and diarrhoea [26%]), whereas some anti-PD-1-associated toxicities seem to be more frequent with the pembrolizumab plus ipililumab combination (eg, pneumonitis [10%]) than with the nivolumab plus ipilumumab combination (pneumonitis [6%]).[8] In the phase 3 CheckMate 067 trial,[8] 55% of patients receiving the combination of nivolumab plus ipilimumab had grade 3–4 treatment-related adverse events after a median follow-up of 9 months, with prevalence increasing to 59% after a minimum follow-up of 28 months,[18] whereas these adverse events occurred in only 45% of patients receiving pembrolizumab plus ipilimumab in this trial after a median follow-up of 17 months. Most immune-mediated adverse events in this trial occurred within the first 6 months of treatment. Furthermore, 72% of patients in this trial were able to receive all four doses of combination therapy, and 67% of all and 79% of grade 3–4 treatment-related adverse events had resolved by data cutoff.

The 61% of patients with an objective response to pembrolizumab plus ipilimumab in this study is higher than the proportion reported for anti-PD-1 monotherapy, which ranges from 20% to 45% depending on the number of previous treatments, and the 15% of patients with a complete response in this study is higher than most other estimates, which range from 2% to 15%, again depending on the number of previous treatments.[4,6,7,9,18] We observed a high proportion of patients with an objective response across all major subgroups, including patients with poor prognostic characteristics or those with a *BRAF*^{V600} mutation or PD-L1-negative tumours. These findings are similar to those observed with nivolumab plus ipilimumab, which seems to have a greater benefit compared with nivolumab monotherapy in patients with PD-L1-negative tumours than in those with PD-L1-positive tumours.[18,24] However, between-study comparisons of subgroups should be interpreted with caution given the absence of power for these analyses in both studies.

The proportions of patients with an objective (61%) and complete (15%) response observed with standard-dose pembrolizumab plus reduced-dose ipilimumab are consistent with those observed in phase 2[17] (objective response 59% and complete response 22%) and 3[18] (59% and 17%) trials of reduced-dose nivolumab plus standard-dose ipilimumab. Cross-trial comparisons should be interpreted with caution given the potential for imbalances in known prognostic and predictive variables, such as serum lactate dehydrogenase concentrations, burden of disease, and baseline PD-L1 expression status.[25,26] Comparison of PD-L1 expression is complicated by use of different assays and definitions of positivity in the KEYNOTE[4,6,27] and CheckMate[8,17,24] trials, resulting in a consistently different proportion of PD-L1 positivity between them. In this phase 1 trial, 25% of patients had an elevated serum lactate dehydrogenase concentration at baseline, a factor strongly associated with poorer response and survival in patients receiving immunotherapy than in those with normal concentrations, whereas the frequency

	Total (n=153)	PD-L1 positive (n=127)	PD-L1 negative (n=24)
Objective response	93 (61% [53–69])	79 (62% [53–71])	12 (50% [29–71])
Disease control*	121 (79% [72–85])	104 (82% [74–88])	15 (63% [41–81])
Best overall response			
Complete response	23 (15%)	18 (14%)	4 (17%)
Partial response	70 (46%)	61 (48%)	8 (33%)
Stable disease	28 (18%)	25 (20%)	3 (13%)
Progressive disease	29 (19%)	21 (17%)	8 (33%)
No assessment done	3 (2%)	2 (2%)	1 (4%)
Time to response (weeks)	12 (12–18)	12 (12–18)	12 (12–16)
Duration of response (weeks)	NR (NE–NE)	NR (NE–NE)	NR (NE–NE)
Responders without subsequent disease progression	87/93 (94%)	73/79 (92%)	12/12 (100%)
Progression-free survival			
Events	52 (34%)	41 (32%)	11 (46%)
Median (months)	NR (NE–NE)	NR (NE–NE)	15·1 (2·8–NE)
Estimate of patients alive and without progression at 12 months (%)	69% (60–75)	70% (61–77)	58% (36–75)

Data are n (% [95% CI]), n (%), median (IQR), or median (95% CI). *Proportion of patients with a best overall response of complete or partial response or stable disease. PD-L1=programmed death ligand 1. NR=not reached. NE=not estimable.

Table 4: **Anti-tumour activity**

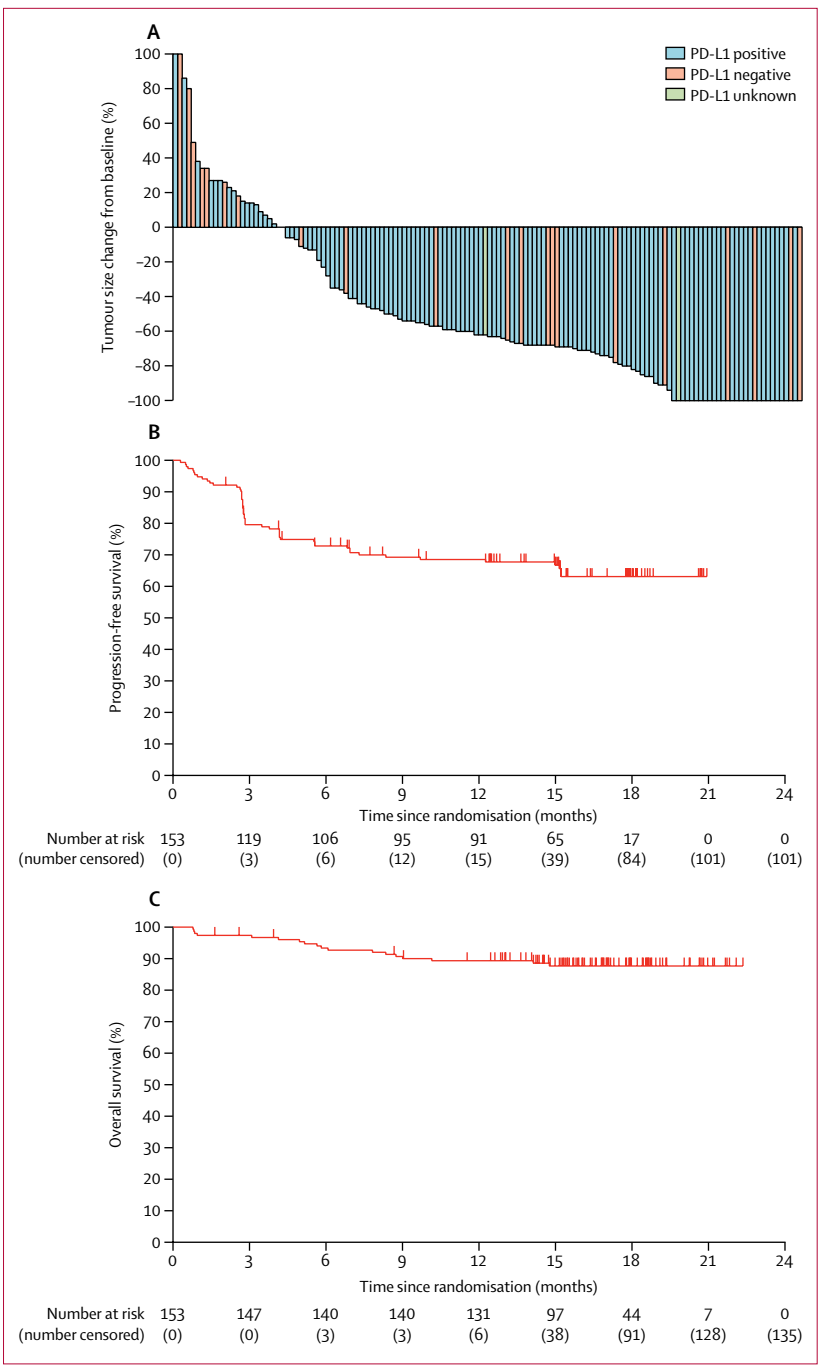

Figure 2: **Anti-tumour activity**
(A) Best percentage change from baseline in the sum of the longest diameters of target lesions in patients who had at least one assessable postbaseline tumour assessment. We truncated changes from baseline of more than 100% at 100%. Kaplan-Meier analysis of (B) progression-free and (C) overall survival in the total population. Tick marks denote censored patients. PD-L1=programmed death ligand 1.

reported in phase 3 trials[6–8,28] of patients with metastatic melanoma ranges from 35% to 40%. Additionally, the relative contribution of PD-1 and CTLA-4 inhibition to long-term efficacy and survival afforded by the combination is unclear. Although CheckMate 067[8] was not powered for the comparison of nivolumab plus ipilimumab with nivolumab alone, the overall survival analysis[18] showed similar estimated overall survival proportions at 1 year (73% for nivolumab plus ipilimumab *vs* 74% for nivolumab alone) and 2 years (64% *vs* 59%). Furthermore, although results from a phase 3 trial[29] of ipilimumab 10 mg/kg versus 3 mg/kg showed a clear dose–response relationship in patients with metastatic melanoma, they do not address the question of whether or not a dose–response relationship exists for anti-CTLA-4 therapy when combined with anti-PD-1 therapy.

The combination of standard-dose pembrolizumab with reduced-dose ipilimumab was highly active, with a tolerable toxicity profile. Further analyses based on longer follow-up than we reported here will be done to define the survival benefit and duration of response of this combination. However, whether or not the reduced dose of ipilimumab used in this study is sufficient to maintain response in the long term and provides anti-tumour activity comparable with that of standard-dose ipilimumab when combined with anti-PD-1 therapy and better than that of anti-PD-1 monotherapy can only be established in an appropriately powered randomised trial. A phase 3 randomised trial of standard-dose nivolumab plus reduced-dose ipilimumab versus reduced-dose nivolumab plus standard-dose ipilimumab for advanced melanoma is underway (NCT02714218) and should help to answer questions regarding the relative efficacy and safety of the two combination strategies. In lieu of the originally planned phase 2 part of the KEYNOTE-029 trial, a randomised cohort exploring pembrolizumab 200 mg every 3 weeks plus four doses of ipilimumab at either 50 mg every 6 weeks or 100 mg every 12 weeks has been opened for enrolment. In an effort to improve the efficacy of anti-PD-1 monotherapy with a minimal increase in toxicity, other pembrolizumab-based combinations are being examined in randomised controlled trials, including combinations with the oncolytic viral therapy talimogene laherparepvec (NCT02263508) and the indoleamine 2,3-dioxygenase inhibitor epacadostat (NCT02752074).

Contributors

GVL, AR, MBA, JAT, FSH, W-JH, SE, and NI conceived, designed, and planned the study. GVL, VA, JSC, MBJ, BMF, CMM, AGH, JAT, FSH, AMM, ADG, RK, BYK, BT, AS, AJL, MI, and MSC acquired data. GVL, AR, JAT, FSH, XS, SE, NI, and MSC analysed data. GVL, VA, JSC, MBJ, BMF, CMM, AR, MBA, JAT, W-JH, FSH, AMM, AS, MI, SE, NI, and MSC interpreted results. GVL, NI, and MSC drafted the manuscript. All authors critically reviewed or revised the manuscript for intellectual content and gave final approval for submission.

Declaration of interests

GVL has served as an advisory board member for Amgen, Array, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, Pierre Fabre, and Roche, and has received honoraria from Bristol-Myers Squibb, Merck Sharp & Dohme, and Roche. VA has served as an advisory board member for and received speakers' fees and travel support from Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis. JSC has received funds from Merck Sharp & Dohme to cover clinical trial expenses for this trial and for serving as an advisory board member. MBJ has received funds from Merck Sharp & Dohme to cover clinical trial expenses for

this trial and to attend an immuno-oncology meeting. CMM has served as an advisory board member for Merck Sharp & Dohme and her institution (the Chris O'Brien Lifehouse) has received travel support, grant support, and honoraria from Merck Sharp & Dohme and an honorarium from Bristol-Myers Squibb for her giving a talk. AR owns stock in Kite Pharma and has received honoraria or consulting fees from Amgen, Merck & Co, Inc, Pfizer, and Roche. MBA has served as a consultant to Bristol-Myers Squibb and Merck & Co, Inc. W-JH has received grants from Bristol-Myers Squibb, GlaxoSmithKline, MedImmune, and Merck & Co, Inc. FSH's institution (the Dana-Farber Cancer Institute) has received clinical trial support for this trial from Merck & Co, Inc, and funding from Bristol-Myers Squibb and he has received personal fees from EMD Serono, Genentech, Merck & Co, Inc, and Novartis for serving as a consultant or advisory board member, has an issued patent for antigen targets, and has a pending patent with royalties to his institution for targeting of MHC class I polypeptide-related sequence A. AMM has served as an advisory board member for Chugai, Merck Sharp & Dohme, Novartis, and Pierre Fabre, and has received honoraria from Bristol-Myers Squibb and Roche. ADG has served as an advisory board member for Bristol-Myers Squibb, Novartis, Pfizer, and Sanofi, has received fees for giving an educational presentation for Merck Sharp & Dohme, and has received travel support from Astellas and Bristol-Myers Squibb. RK has served as an advisory board member for and his institution (Macquaire University) has received funds from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, and Teva, and he has received a grant from Bristol-Myers Squibb. XS, SE, and NI are employees of Merck Sharp & Dohme, a subsidiary of Merck & Co, Inc. SE and NI hold stock in Merck & Co, Inc. NI owns stock in GlaxoSmithKline. MSC has served as an advisory board member for and received honoraria from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, and Novartis. All other authors declare no competing interests.

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