Combined nivolumab and ipilimumab with or without stereotactic body radiation therapy for advanced Merkel cell carcinoma: a randomised, open label, phase 2 trial

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Summary

Background Merkel cell carcinoma is among the most aggressive and lethal of primary skin cancers, with a high rate of distant metastasis. Anti-programmed death receptor 1 (anti-PD-1) and programmed death ligand 1 (PD-L1) monotherapy is currently standard of care for unresectable, recurrent, or metastatic Merkel cell carcinoma. We assessed treatment with combined nivolumab plus ipilimumab, with or without stereotactic body radiotherapy (SBRT) in patients with advanced Merkel cell carcinoma as a first-line therapy or following previous treatment with anti-PD-1 and PD-L1 monotherapy.

Methods In this randomised, open label, phase 2 trial, we randomly assigned adults from two cancer sites in the USA (one in Florida and one in Ohio) to group A (combined nivolumab and ipilimumab) or group B (combined nivolumab and ipilimumab plus SBRT) in a 1:1 ratio. Eligible patients were aged at least 18 years with histologically proven advanced stage (unresectable, recurrent, or stage IV) Merkel cell carcinoma, a minimum of two tumour lesions measureable by CT, MRI or clinical exam, and tumour tissue available for exploratory biomarker analysis. Patients were stratified by previous immune-checkpoint inhibitor (ICI) status to receive nivolumab 240 mg intravenously every 2 weeks plus ipilimumab 1 mg/kg intravenously every 6 weeks (group A) or the same schedule of combined nivolumab and ipilimumab with the addition of SBRT to at least one tumour site (24 Gy in three fractions at week 2; group B). Patients had to have at least two measurable sites of disease so one non-irradiated site could be followed for response. The primary endpoint was objective response rate (ORR) in all randomly assigned patients who received at least one dose of combined nivolumab and ipilimumab. ORR was defined as the proportion of patients with a complete response or partial response per immune-related Response Evaluation Criteria in Solid Tumours. Response was assessed every 12 weeks. Safety was assessed in all patients. This trial is registered with ClinicalTrials.gov, NCT03071406.

Findings 50 patients (25 in both group A and group B) were enrolled between March 14, 2017, and Dec 21, 2021, including 24 ICI-naive patients (13 [52%] of 25 group A patients and 11 [44%] of 25 group B patients]) and 26 patients with previous ICI (12 [48%] of 25 group A patients and 14 [56%] of 25 group B patients]). One patient in group B did not receive SBRT due to concerns about excess toxicity. Median follow-up was 14·6 months (IQR 9·1–26·5). Two patients in group B were excluded from the analysis of the primary endpoint because the target lesions were irradiated and so the patients were deemed non-evaluable. Of the ICI-naive patients, 22 (100%) of 22 (95% CI 82–100) had an objective response, including nine (41% [95% CI 21–63]) with complete response. Of the patients who had previously had ICI exposure, eight (31%) of 26 patients (95% CI 15–52) had an objective response and four (15% [5–36]) had a complete response. No significant differences in ORR were observed between groups A (18 [72%] of 25 patients) and B (12 [52%] of 23 patients; p=0·26). Grade 3 or 4 treatment-related adverse events were observed in 10 (40%) of 25 patients in group A and 8 (32%) of 25 patients in group B.

Interpretation First-line combined nivolumab and ipilimumab in patients with advanced Merkel cell carcinoma showed a high ORR with durable responses and an expected safety profile. Combined nivolumab and ipilimumab also showed clinical benefit in patients with previous anti-PD-1 and PD-L1 treatment. Addition of SBRT did not improve efficacy of combined nivolumab and ipilimumab. The combination of nivolumab and ipilimumab represents a new first-line and salvage therapeutic option for advanced Merkel cell carcinoma.

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Research in context

Evidence before this study

Merkel cell carcinoma is a rare but aggressive skin cancer, driven by Merkel cell polyomavirus or ultraviolet light exposure, with a high rate of metastasis and poor prognosis. We searched PubMed on Feb 7, 2022, and on May 20, 2022, for reports published in English since database inception using the search term "Merkel cell carcinoma", combined with "immunotherapy" or "immune checkpoint inhibitor". Using the term "Merkel cell carcinoma", we also searched abstracts published in English from the American Society of Clinical Oncology from May 20, 2015, to June 10, 2022, and the European Society for Medical Oncology from Sept 25, 2015, to Dec 11, 2021. We identified case reports and retrospective studies as well as four prospective studies that assessed immune-checkpoint inhibitors in patients with Merkel cell carcinoma with advanced stage disease. Since 2015, a major breakthrough with anti-programmed death receptor 1 (anti-PD-1) and programmed death ligand 1 (PD-L1) therapy has shifted paradigms in the management of Merkel cell carcinoma. With an objective response rate (ORR) ranging from 33% to 58% with durable responses, avelumab and pembrolizumab were approved by the US Food and Drug Administration as first-line therapy, and are currently the standard of care as per the National Comprehensive Cancer Network and European consensus-based interdisciplinary guidelines. Despite the immense success of anti-PD-1 and PD-L1 therapy, patients who are refractory to these agents represent a major clinical challenge with few therapeutic options. Multiple chemotherapy regimens are clinically active in Merkel cell carcinoma, but responses are short lived. Further, there has not been much success with targeted therapies. Therefore, strategies to improve upon the efficacy of anti-PD-1 and PD-L1 monotherapy is of crucial importance. Targeting cytotoxic T lymphocyte-associated antigen 4 (CTLA4) in combination with anti-PD-1 and PD-L1 therapy has been tested in several cancers with promising outcomes. Retrospective institutional case series published since 2019 have reported some clinical activity of combined nivolumab and ipilimumab among patients with Merkel cell carcinoma who have previously progressed on anti-PD-1 and PD-L1 monotherapy, but prospective studies of this combination have not been previously done. Additionally, the capacity of radiotherapy to induce systemic antitumour immune responses has been under intense research with conflicting outcomes since 2009. Although radiotherapy has an integral role in locoregional management of early-stage Merkel cell carcinoma, its potential effect in augmenting systemic immunotherapy has not been previously investigated in advanced Merkel cell carcinoma.

Added value of this study

This randomised, phase 2 trial with two experimental groups investigated the efficacy of combined nivolumab and ipilimumab versus combined nivolumab and ipilimumab plus stereotactic body radiotherapy (SBRT) in a population of patients with unresectable, recurrent, or metastatic Merkel cell carcinoma. Patients were stratified by previous exposure to immune-checkpoint inhibitor (ICI) treatment. To our knowledge, this is the first prospective study showing the efficacy of combined anti-PD-1 and anti-CTLA4 in Merkel cell carcinoma. Anti-CTLA4 has not been previously investigated in Merkel cell carcionoma. The clinical activity of combined nivolumab and ipilimumab that was shown both in the first-line and salvage setting suggests that CTLA4 could represent a major immune resistance mechanism in Merkel cell carcinoma, and the current standard of care with anti-PD-1 and anti-PD-L1 monotherapy could benefit from targeting this pathway. Addition of SBRT did not enhance the therapeutic efficacy of combined nivolumab and ipilimumab, suggesting that the clinical benefit of SBRT beyond the radiation field is unlikely in Merkel cell carcinoma. However, an excellent local control was achieved in the irradiated lesions even among patients who were progressing on the protocol treatment, and there is rationale for studying de-escalated radiation dose used in this study for early-stage Merkel cell carcinoma.

Implications of all the available evidence

Building upon the previous success of anti-PD-1 and anti-PD-L1 monotherapy in the management of Merkel cell carcinoma, escalated immunotherapy with combined nivolumab and ipilimumab shows a high objective response rate with durable responses and manageable toxicity profiles among patients who have not previously been exposed to a systemic therapy, thus expanding the first-line therapeutic options for advanced Merkel cell carcinoma. Additionally, patients with Merkel cell carcinoma who have progressed on the first-line anti-PD-1 and anti-PD-L1 monotherapy have been a clinical challenge and have few therapeutic options. Together with previous retrospective cohort studies, this prospective study provides a rationale for using combined nivolumab and ipilimumab as a salvage therapy in this patient cohort refractory to anti-PD-1 and anti-PD-L1 monotherapy. Notably, the results of our study lends support to the therapeutic framework of combining immune checkpoint inhibitors to improve management of Merkel cell carcinoma and other cancers.

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Introduction

Merkel cell carcinoma is one of the most aggressive and lethal primary skin cancers, with a high rate of distant metastases and poor survival outcome.[1,2] Merkel cell carcinoma pathogenesis is driven by Merkel cell polyomavirus or ultraviolet light exposure.[1,3] Since 2016, a major breakthrough in Merkel cell carcinoma was achieved with immune-checkpoint inhibitors (ICI) targeting programmed death ligand 1 (PD-L1) and programmed death receptor 1 (PD-1). The US Food and Drug Administration (FDA) approved, for the treatment of advanced Merkel cell carcinoma, avelumab in 2017 and pembrolizumab in 2018. Avelumab was associated with an objective response rate (ORR) of 39·7% (95% CI

30·7–49·2) as first-line therapy and 33% (23·3–43·8%) in patients with chemotherapy-refractory metastatic Merkel cell carcinoma, with durable responses.[4–6] First-line therapy with pembrolizumab was associated with an ORR of 58% (95% CI 43·2–71·8) in a phase 2 study of 50 patients with advanced Merkel cell carcinoma,[7,8] with the majority of responses being durable.[7] Pembrolizumab was effective in both Merkel cell polyomavirus-positive and ultraviolet-induced Merkel cell polyomavirus-negative Merkel cell carcinoma.[8] Although these studies have established anti-PD-1 and PD-L1 monotherapy as standard of care in advanced Merkel cell carcinoma,[4,8] the majority of patients for whom anti-PD1 and PD-L1 monotherapy fails have few therapeutic options, and identifying strategies to overcome immunological barriers leading to tumour resistance to anti-PD-1 and PD-L1 monotherapy is of pivotal importance in the management of Merkel cell carcinoma.

Combining PD-1 and PD-L1 blockade with modulation of alternative immunological targets has been the mainstay of recent innovation in cancer immunotherapy. Notably, cytotoxic T lymphocyte-associated antigen 4 (CTLA4), expressed on activated effector and regulatory T cells, dampens antitumour immune responses by disrupting CD28 costimulation. Ipilimumab, an anti-CTLA4 antibody, was the first FDA-approved ICI for cancer. Although the single agent activity of ipilimumab has not been extensively investigated in Merkel cell carcinoma, the efficacy of the nivolumab and ipilimumab combination has been shown in several tumour types.[9–11] Cancer immunotherapy could also be combined with conventional cytotoxic therapy to harness antitumour immune responses elicited by immunogenic cell death.[12] Radiotherapy in combination with ICI has previously shown clinical benefit.[13,14] Further, Merkel cell carcinoma is profoundly radiosensitive and radiotherapy has an established role in the locoregional management of Merkel cell carcinoma;[15] the addition of stereotactic body radiotherapy (SBRT) to ICI is therefore worthy of further investigation. Notably, the abscopal effect of radiotherapy has been most extensively studied in combination with CTLA4 blockade. Subablative hypofractionated radiotherapy, ranging from 21 Gy to 24 Gy and delivered over three fractions, as well as CTLA4 blockade, are thought to induce a priming event for eliciting anti-tumour immune responses, and synergy of these two modalities has been shown in multiple preclinical studies.[16] Interestingly, PD-L1 expression has been proposed as the major mechanism of resistance to the combination of radiotherapy and ipilimumab.[17] In this context, there is a strong rationale to test whether ipilimumab will potentiate the efficacy of SBRT and nivolumab in Merkel cell carcinoma. Therefore, we did a phase 2, randomised, open-label trial with two experimental groups to evaluate the safety and efficacy of nivolumab and ipilimumab with or without SBRT in advanced Merkel cell carcinoma.

Methods

Study design

In this randomised, open-label, phase 2 study, patients were enrolled at the Moffitt Cancer Center (Florida, USA) and Ohio State University James Cancer Hospital and Solove Research Institute (Ohio, USA). The study was designed with two experimental groups to determine the clinical efficacy of combined nivolumab and ipilimumab and the role of SBRT in augmenting combined nivolumab and ipilimumab, as first-line therapy or following previous ICI failure.

The protocol was approved by the institutional review board at each participating center, and the study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Good Clinical Practice guidelines. All patients provided written informed consent before study entry.

Participants

Eligible patients were aged at least 18 years with unresectable, recurrent, or stage IV (according to the American Joint Committee on Cancer, seventh edition) Merkel cell carcinoma. Patients of any stage were also eligible if disease was either unresectable or recurrent. Participants were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and a minimum of two histologically proven measurable tumour lesions measurable by CT, MRI, or clinical exam (to ensure the presence of at least one unirradiated lesion to assess response). Previous chemotherapy or immunotherapy given in either adjuvant or unresectable or metastatic settings was allowed if new or progressive measurable sites of disease were present at enrolment. Patients with a history of radiotherapy were eligible if current measurable lesions were not treated with radiotherapy. To be eligible for the study, participants were required to have tumour tissue from the core biopsy or resected site of disease available for biomarker analyses. Key exclusion criteria were history of grade 3 toxicity or use of infliximab with previous immunotherapy, active brain metastasis, autoimmune disease or other conditions requiring systemic treatment with corticosteroids (>10 mg daily prednisone or equivalent) or other immuno-suppressive medications, or history of non-Merkel cell carcinoma malignancies (except indolent diseases such as chronic lymphocytic leukemia that did not require active therapy or where cander was adequately treated and in complete remission).

Randomisation and masking

Eligible patients were randomly assigned with a ratio of 1:1, stratified based on previous ICI use (ICI naive or previous ICI use). We used the Moffitt Subject Registration and Randomization programme to randomly assign patients; this is a web-delivered application that records participant registrations and provides randomisation assignment. Patients were not

masked to study group. Patients were stratified on the basis of whether or not they had received previous immunotherapy with anti-PD-1 and PD-L1 monotherapy. All treatment allocation was unblinded.

Procedures

Patients were treated with intravenous nivolumab 240 mg every 2 weeks and intravenous ipilimumab 1 mg/kg every 6 weeks (figure 1). Patients enrolled into group B also received SBRT to at least one tumour site at a dose of 24 Gy in three fractions during week 2, beginning before the second nivolumab infusion. Non-skin lesions were treated with SBRT delivered on 3 consecutive days, and skin lesions were treated every other day. Simultaneous integrated boost or dose-painting was allowed to meet normal tissue dose constraints. At least one measurable lesion was not to be irradiated to evaluate response outside the radiation field. Patients received systemic treatment with nivolumab and ipilimumab until disease progression, unacceptable toxicity, or withdrawal of consent. Patients were allowed to continue treatment after disease progression as long as investigator-assessed clinical benefit was present and the patient was tolerating the study drugs. All patients underwent CT scanning of the thorax, abdomen, and pelvis (as well as any other areas with target lesions) at the time of screening and every 12 weeks after starting therapy. Evaluations of scans according to immune-related Response Evaluation Criteria in Solid Tumours (irRECIST)[18] were done by radiologists, who had no further involvement in the study, at the institutional level. irRECIST forms were signed off by the Principal Investigator at Moffitt (SK) and the site Principal Investigator at Ohio State University (DB). Response assessment was based on non-irradiated target lesions. Adverse events were recorded according to National Cancer Institute Common Terminology Criteria for Adverse Events version 4.0.[20]

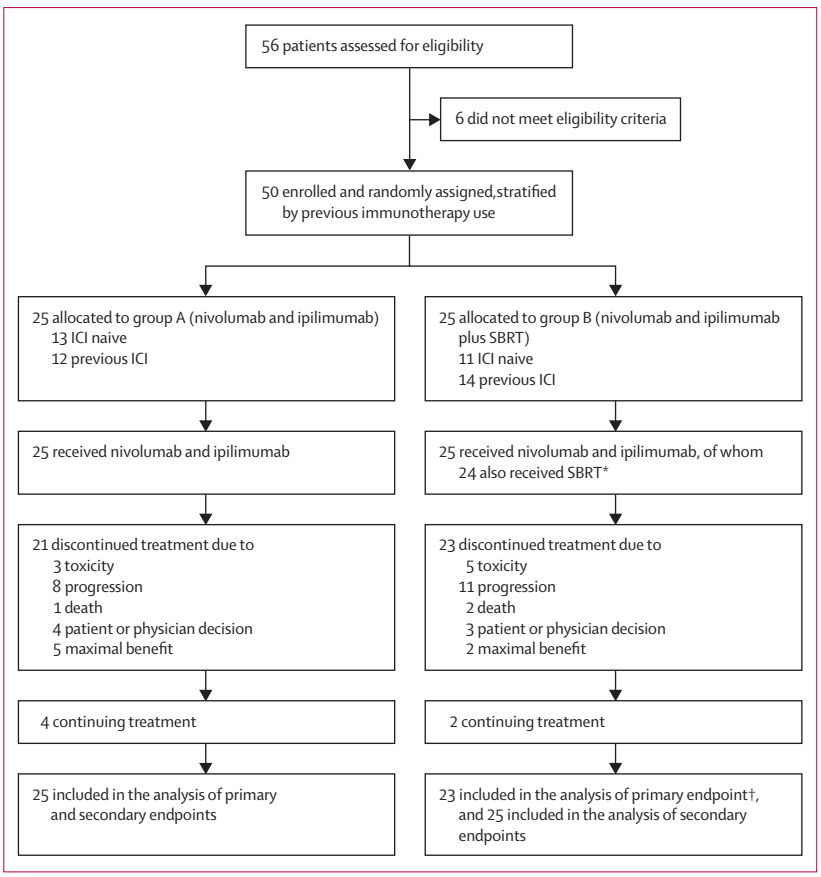

Figure 1: **Flowchart of study population**
SBRT=stereotactic body radiation therapy. *One patient did not receive SBRT due to concern about excess toxicity from overlap with the previous radiation field. †Two patients received SBRT to the target lesion and were excluded from the objective response rate analysis.

Outcomes

Radiological and physical examination assessments according to irRECIST were used to determine treatment responses. The primary endpoint was ORR, which was defined as the percentage of randomly assigned patients who had a complete or partial response among all the patients who received at least one dose of combined nivolumab and ipilimumab. Best overall response, complete response, partial response, stable disease, and progressive disease were defined per irRECIST as specified in the protocol.[18] Key secondary endpoints were progression-free survival (PFS; defined as the interval from the date of the first dose of combined nivolumab and ipilimumab to the date of disease progression or death, whichever occurred first), overall survival (OS; defined as the interval from the date of the first dose of combined nivolumab and ipilimumab to the date of death), local control (LC) of irradiated tumours (defined as the interval from the date of SBRT to the date of progression of the irradiated lesion), safety, and to evaluate whether PD-L1 expression is a predictive biomarker for ORR. Secondary endpoints regarding patient reported outcomes, including the Health Related Quality of Life as assessed by European Organisation for Research and Treatment of Cancer QLQ-C30, will be reported separately. Analysis of the Merkel cell polyomavirus status was planned as an exploratory biomarker analysis. Duration of response (DOR), which was not a prespecified endpoint but a post-hoc analysis, was defined as the interval from the date of first response to the date of disease progression or death. Subgroup analysis of the previous-ICI cohort comparing patients previously exposed to PD-L1 blockade versus PD-1 blockade was also performed as a post-hoc analysis.

Statistical analysis

Patients who received at least one dose of combined nivolumab and ipilimumab were included in the primary, secondary, and safety analysis. The best overall response was defined as the best response recorded between the start of the treatment until disease progression. Clopper–Pearson

	Total (n=50)	Group A (combined nivolumab and ipilimumab) (n=25)	Group B (combined nivolumab and ipilimumab plus SBRT) (n=25)	p value
Age, years	73 (67–81)	74 (66–81)	73 (68–76)	0·81
Sex	..	..	..	0·99
Female	11 (22%)	5 (20%)	6 (24%)	..
Male	39 (78%)	20 (80%)	19 (76%)	..
Race	..	..	..	0·99
White	50 (100%)	25 (100%)	25 (100%)	..
Other	0	0	0	..
ECOG performance status	..	..	..	0·99
0	23 (46%)	11 (44%)	12 (48%)	..
1	27 (54%)	14 (56%)	13 (52%)	..
Disease stage	..	..	..	0·32
IIIB	12 (24%)	4 (16%)	8 (32%)	..
IV	38 (76%)	21 (84%)	17 (68%)	..
Primary tumour site	..	..	..	0·48
Head and neck	16 (32%)	11 (44%)	5 (20%)	..
Trunk	2 (4%)	1 (4%)	1 (4%)	..
Extremities	26 (52%)	11 (44%)	15 (60%)	..
Unknown primary	6 (12%)	2 (8%)	4 (16%)	..
Metastatic stage*	..	..	..	0·26
M0	12 (24%)	4 (16%)	8 (32%)	..
M1a	19 (38%)	12 (48%)	7 (28%)	..
M1b	0	0	0	..
M1c	19 (38%)	9 (36%)	10 (40%)	..
Number of distant metastatic sites	..	..	..	0·81
0	12 (24%)	4 (16%)	8 (32%)	..
1–2	16 (32%)	9 (36%)	7 (28%)	..
3–4	14 (28%)	9 (36%)	5 (20%)	..
>5	7 (14%)	3 (12%)	4 (16%)	..
Lactate dehydrogenase concentration				
Normal	26 (52%)	10 (40%)	16 (64%)	0·16
Elevated	24 (48%)	15 (60%)	9 (36%)	
Previous immunotherapy status†	..	..	..	0·78
ICI naive	24 (48%)	13 (52%)	11 (44%)	..
Previous ICI	26 (52%)	12 (48%)	14 (56%)	..
Previous chemotherapy status‡	..	..	..	0·99
Chemotherapy naive	45 (90%)	23 (92%)	22 (88%)	..
Previous chemotherapy	5 (10%)	2 (8%)	3 (12%)	..

Data are n (%) or median (IQR). ECOG=Eastern Cooperative Oncology Group. ICI=immune-checkpoint inhibitor. SBRT=stereotactic body radiotherapy. *According to the American Joint Committee on Cancer, seventh edition. †21 patients had disease progression while on ICI: two patients progressed after discontinuation of these agents following initial response, and three patients received ICI as adjuvant therapy and subsequently relapsed. ‡Four patients received chemotherapy before any ICI, and one patient received chemotherapy following previous ICI.

Table 1: **Patient characteristics**

exact CIs were generated for the response rates. Two-sample proportion test and the Bayesian posterior probability were used for comparison of response rate between the two groups. Subgroup analysis was done on the basis of the ICI stratification. PFS, OS, DOR, and LC were estimated with the Kaplan–Meier method.[21] A Bayesian pick-the-winner design[19] was used with each group using a Simon's Mini-Max two-stage design with 10% for type I and II error rates, which required three or more responders in the first stage of 16 patients to advance to the second stage for a total of 24 patients. Interim analysis was planned following the completion of the first stage to evaluate efficacy and unexpected drug-related adverse events. If the total number responding was six or less, we would conclude that the treatment was not effective. We would consider group B (combined nivolumab and ipilimumab plus SBRT) superior if the posterior probability of a higher response rate for group B than for group A (combined nivolumab and ipilimumab) was more than 80% on the basis of a non-informative prior of β distribution, β(1,1). Each group had 25 patients with 24 efficacy-evaluable patients, for a total of 50 patients. R version 4.1.2 was used for the statistical analysis. This trial is registered with ClinicalTrials.gov, NCT03071406.

Role of the funding source

The funder reviewed the scientific accuracy of the protocol and publication, but otherwise had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

Results

A total of 50 patients with unresectable, recurrent, or stage IV Merkel cell carcinoma were enrolled between March 14, 2017, and Dec 21, 2021. All patients received protocol-assigned treatment except one patient in group B who did not receive SBRT due to concerns about excess toxicity from overlap with the previous radiation field (figure 1). Median age was 74 years (IQR 66–81) for group A and 73 years (IQR 68–76) for group B. 14 (56%) of 25 patients in group A and 13 (52%) of 25 patients in group B had had an ECOG performance status of 1, and the remainder had an ECOG performance status of 0. Four (16%) of patients in group A and 8 (32%) of patients in group B had recurrent stage IIIB disease; the remainder were stage IV at the time of enrolment (table 1). Notably, 12 (48%) of patients in group A and 14 (56%) of patients in group B were previously treated with pembrolizumab or avelumab (previous-ICI cohort; table 1). Of the 26 patients in the previous-ICI cohort, 21 (81%) patients had disease progression while on pembrolizumab or avelumab, two (10%) patients progressed after discontinuation of these agents following initial response, and three (12%) patients received ICI as adjuvant therapy and subsequently relapsed (table 1). Two (8%) patients in group A and 3 (12%) patients in group B had previously received chemotherapy, all of whom also received previous ICI. Randomisation yielded reasonable balance of demographic and clinical factors in both groups (p>0·05; table 1).

Both groups completed the two stages of accrual with 25 patients each (figure 1). In group B, two ICI-naive patients received SBRT to the only target lesion that was

	Total		Group A (combined nivolumab and ipilimumab)		Group B (combined nivolumab and ipilimumab plus SBRT)	
	ICI naive (n=24)	Previous ICI (n=26)	ICI naive (n=13)	Previous ICI (n=12)	ICI naive (n=11)	Previous ICI (n=14)
ORR (95% CI)	100 (82–100)	31 (15–52)	100% (72–100)	42% (16–71)	100% (63–100)	21% (6–51)
BOR						
Complete response	9/22 (41%)	4 (15%)	7 (54%)	3 (25%)	2/9 (22%)	1 (7%)
Partial response*	13/22 (59%)	4 (15%)	6 (46%)	2 (17%)	7/9 (78%)	2 (14%)
Stable disease	0	1 (4%)	0	1 (8%)	0	0
Progressive disease	0	17 (65%)	0	6 (50%)	0	11 (79%)
Non-evaluable†	2	0	0	0	2	0
Progression following initial response	2 (9%)	4 (50%)	2 (15%)	3/5 (60%)	0	1/3 (33%)
Median DOR, months (95% CI)‡	NE (34–NE)	11 (5–NE)	NE (33·9–NE)	15·1 (6·6–NE)	NE	4·9 (2·8–NE)

Data are n (%) unless otherwise stated. Percentages are rounded to the nearest whole number. BOR=best overall response. ICI=immune-checkpoint inhibitor. ORR=objective response rate. SBRT=stereotactic body radiotherapy. DOR=duration of response. NE=non-estimable. *Two partial responders in the previous-ICI cohort had unconfirmed partial responses. †Two patients deemed non-evaluable as the target lesion was irradiated. ‡Includes 30 responders with at least 6 months of follow-up.

Table 2: **Objective response and durability of response**

measurable by irRECIST. Target lesions in both patients responded. In one patient, both the irradiated target lesion and the non-irradiated non-target lesion completely resolved. In the second patient, the irradiated lesion showed partial response and the non-irradiated non-target lesions remained stable and without new lesions at 9 months. Because the target lesions were irradiated, these two patients were deemed non-evaluable and excluded from analysis of ORR.

18 (72%) of 25 patients in group A and 12 (52%) of 23 patients in group B had a response, with no statistical difference between the two groups (p=0·26 by two-sample proportion test; 0·2 for the Bayesian posterior probability of higher response rate in group B than in group A). Pooled analysis stratified by ICI status showed that, of the patients who were ICI naive, 22 (100% [95% CI 82–100]) of 22 evaluable patients had an objective response, nine (41% [21–63]) with complete response (table 2). By contrast, of the patients who had previously received anti-PD-1 and PD-L1 monotherapy treatment, eight (31% [95% CI 15–52]) of 26 patients had an objective response, and four (15% [5–36]) with complete response (table 2). Representative CT images of a long-term survivor following response to combined nivolumab and ipilimumab is shown in the appendix (p 1). Of the 30 responders, response was confirmed on a subsequent evaluation in 28 patients. Two responding patients in the previous-ICI cohort had unconfirmed partial responses: one patient subsequently progressed, and one patient died before the confirmation scan (table 2).

Following initial response, two (9%) of 22 responders in the ICI-naive cohort subsequently progressed, and four (50%) of eight responders progressed in the previous-ICI cohort (table 2, figure 2A). All apart from one patient were still receiving protocol treatment at the time of progression. Additionally, one responder in the previous-ICI cohort died following initial response unrelated to the disease status or toxicity. Median duration of response, in months, was not reached (95% CI 33·9–not evaluable [NE]) in the ICI-naive cohort and was 10·8 months [4·9–NE] in the previous-ICI cohort. Best overall response, disease progression, and death are summarised in figure 2A and 2B. To gain further insight into the durability of response, a spider plot of target lesion size measurement for each patient was generated. Most patients had durable tumour regression following initial response (figure 2C).

With a median follow-up of 14·6 months (IQR 9·1–26·5), median PFS was not reached for the ICI-naive cohort in either group. For the previous-ICI cohort, median PFS was 4·2 months (95% CI 1·5–NE; group A) and 2·7 months (2·2–7·6; group B; figure 3A). Median OS was not reached for the ICI-naive cohort in either group, and median OS for the previous-ICI cohort was 14·9 months (95% CI 0·3–NE; group A) and 9·7 months (5·0–NE; group B; figure 3B). Median time-to-event for local control was 12·6 months (IQR 8·8–15.9) . Local progression of an irradiated lesion was not observed in any patients treated with SBRT (figure 3C). PD-L1 expression status in relation to response is in the appendix.

All 50 patients accrued on the trial were included in the safety analysis. Adverse effects were primarily attributable to the combination of nivolumab and ipilimumab, and minimal SBRT-related toxicities were observed. Treatment-related adverse events of any grade occurred in 45 (90%) of 50 patients (table 3). The most common adverse event was fatigue. Grade 3 or 4 treatment-related adverse events were observed in 10 (40%) of 25 patients in group A and 8 (32%) of 25 patients in group B (table 3). Five patients had grade 4 treatment-related adverse events: four had elevated pancreatic enzymes and one had hyponatraemia with acute kidney injury (table 3). Eight (16%) of 50 patients discontinued the protocol treatment due to toxicity. Three (6%) of 50 patients with

See Online for appendix

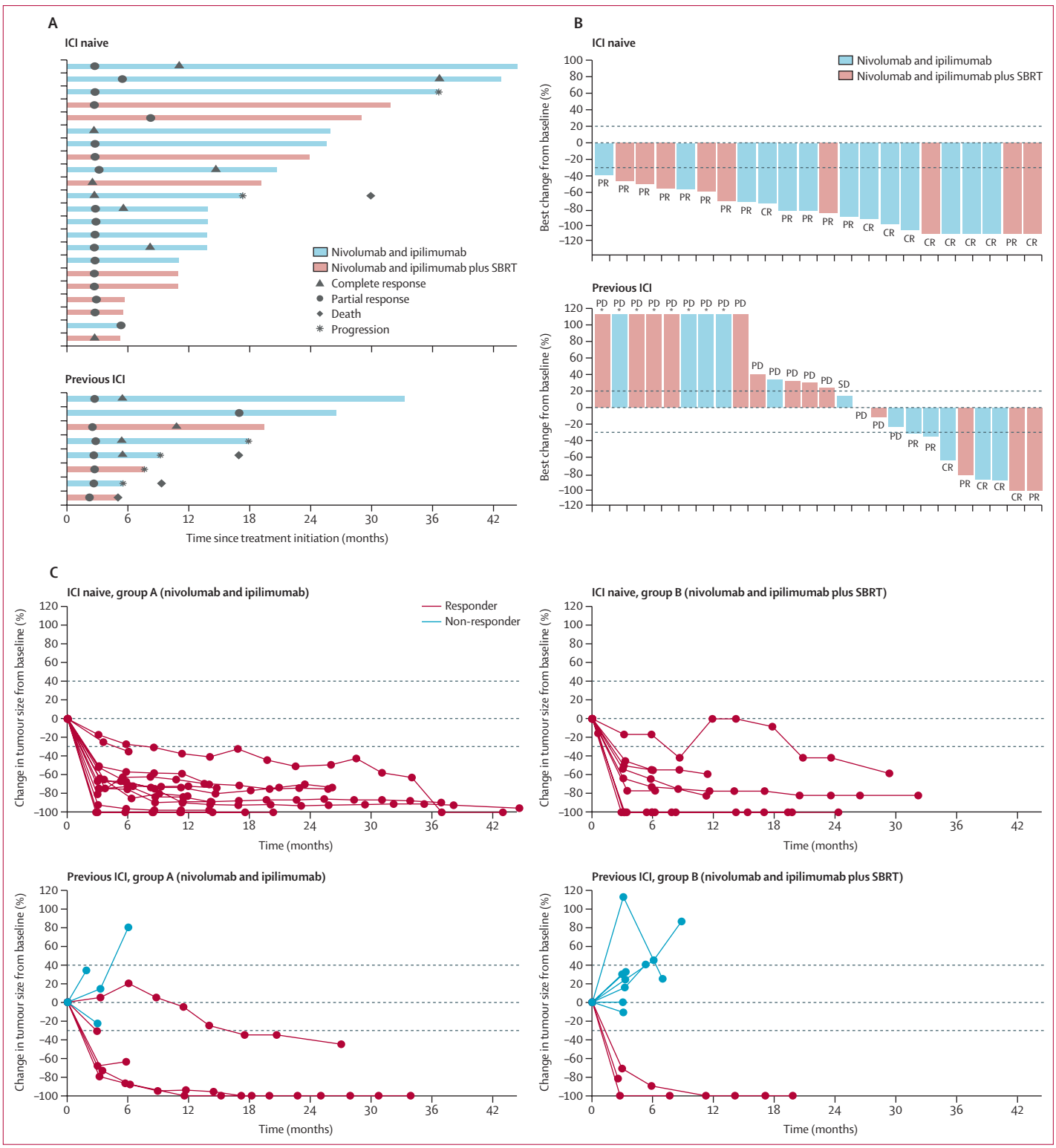

***Figure 2*: Duration of response (A), best response percent change from baseline (B), and change in sum of target lesion diameters from baseline in individual patients over time (C)**
In A, time to response and duration of response were measured in 30 patients with a clinical response (complete or partial). B does not include two patients who were excluded as the target lesions were irradiated. C does not include two patients with irradiated target lesion or eight patients with clinical progression before the first planned restaging. Progression is defined as an increase of 20% or more in the sum of diameters of target lesions or appearance of a new lesion. PR=partial response. CR=complete response. SD=stable disease. *Eight patients had clinical progression before the first planned restaging.

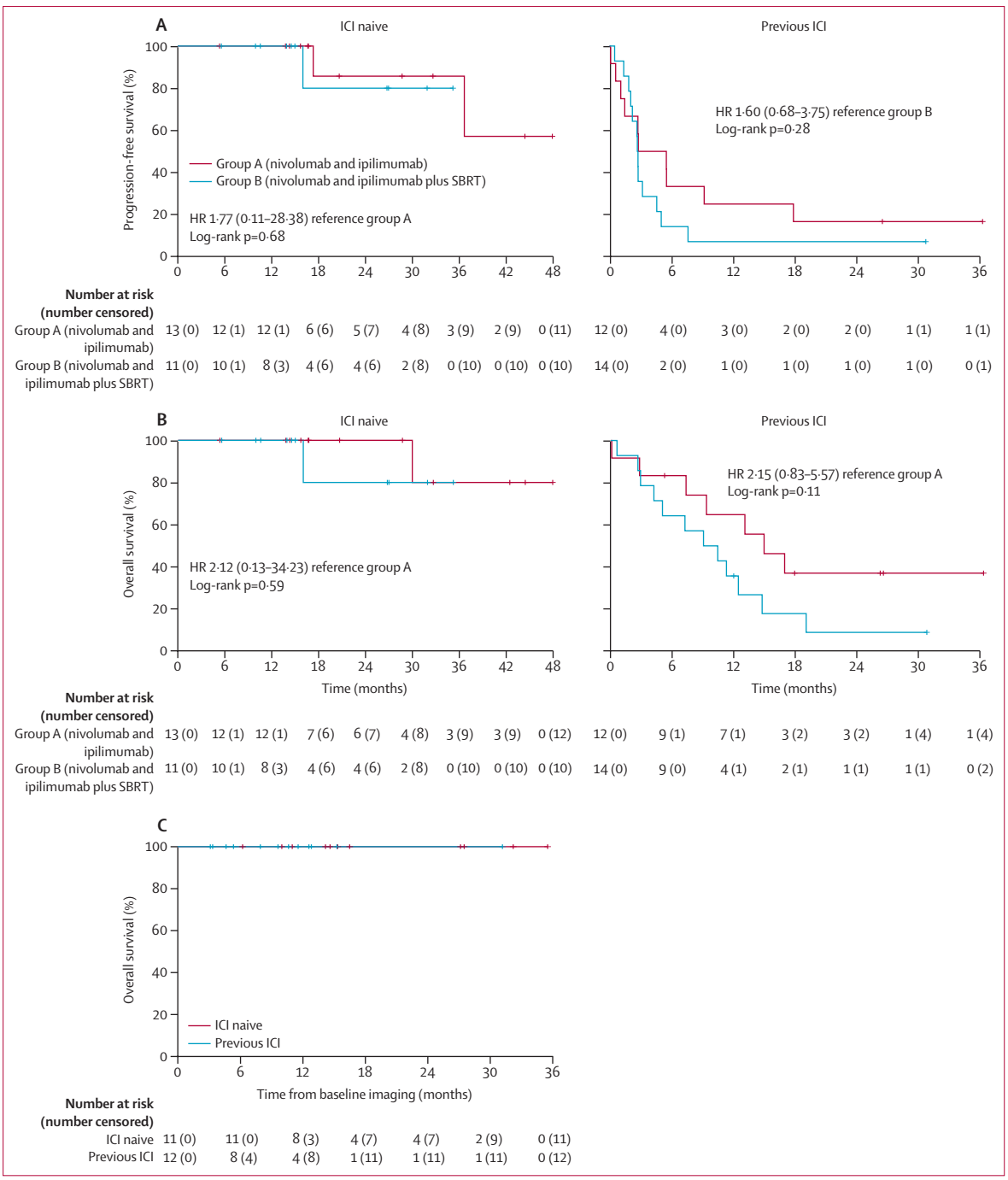

Figure 3: **Progression-free survival for ICI-naive cohorts and previous-ICI cohorts (A), overall survival for ICI-naive cohorts and previous-ICI cohorts (B), and local control of irradiated lesions in group B (C)**
HR=hazard ratio. ICI=immune-checkpoint inhibitor.

rapidly progressive disease after previous-ICI treatment died before the first planned restaging. In these cases, death was attributed to disease progression and not to treatment-related toxicity; all these patients were considered to have progressive disease as best overall response.

Discussion

Antibodies targeting the PD-1 and PD-L1 pathway are active in Merkel cell carcinoma, one of the most immunogenic human cancers, with ORR ranging from 33–58% and durable responses.[4,8,22] However, recurrence after, or refractoriness to, first-line anti-PD-1 and PD-L1

	Total (n=50)			Group A (combined nivolumab and ipilimumab; n=25)			Group B (combined nivolumab and ipilimumab plus SBRT; n=25)		
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3	Grade 4
Any	27 (54%)	13 (26%)	5 (10%)	11 (44%)	7 (28%)	3 (12%)	16 (64%)	6 (24%)	2 (8%)
Fatigue	31 (62%)	1 (2%)	0	18 (72%)	1 (4%)	0	13 (52%)	0	0
Pruritus	20 (40%)	0	0	11 (44%)	0	0	9 (36%)	0	0
Diarrhoea	20 (40%)	2 (4%)	0	9 (36%)	1 (4%)	0	11 (44%)	1 (4%)	0
Rash or dermatitis	19 (38%)	1 (2%)	0	11 (44%)	0	0	8 (32%)	1 (4%)	0
Nausea	16 (32%)	0	0	9 (36%)	0	0	7 (28%)	0	0
Elevated pancreatic enzymes	14 (28%)	2 (4%)	4 (8%)	12 (48%)	0	2 (8%)	2 (8%)	2 (8%)	2 (8%)
Cough	12 (24%)	0	0	6 (24%)	0	0	6 (24%)	0	0
Anorexia	11 (22%)	0	0	3 (12%)	0	0	8 (32%)	0	0
Edema limbs	10 (20%)	0	0	5 (20%)	0	0	5 (20%)	0	0
Dyspnoea	9 (18%)	0	0	4 (16%)	0	0	5 (20%)	0	0
Dizziness	9 (18%)	0	0	5 (20%)	0	0	4 (16%)	0	0
Hypothyroidism	9 (18%)	0	0	5 (20%)	0	0	4 (16%)	0	0
Hyperkalaemia	8 (16%)	0	0	5 (20%)	0	0	3 (12%)	0	0
Weight loss	8 (16%)	0	0	5 (20%)	0	0	3 (12%)	0	0
Arthralgia	8 (16%)	3 (6%)	0	4 (16%)	2 (8%)	0	4 (16%)	1 (4%)	0
Elevated transaminases	8 (16%)	3 (6%)	0	4 (16%)	3 (12%)	0	4 (16%)	0	0
Vomiting	7 (14%)	0	0	4 (16%)	0	0	3 (12%)	0	0
Abdominal Pain	7 (14%)	0	0	2 (8%)	0	0	5 (20%)	0	0
Hyponatraemia	6 (12%)	1 (2%)	1 (2%)	3 (12%)	1 (4%)	1 (4%)	3 (12%)	0	0
Adrenal insufficiency	5 (10%)	1 (2%)	0	4 (16%)	1 (4%)	0	1 (4%)	0	0
Dysgeusia	4 (8%)	1 (2%)	0	4 (16%)	0	0	0	1 (4%)	0
Anaemia	3 (6%)	1 (2%)	0	3 (12%)	0	0	0	1 (4%)	0
Colitis	3 (6%)	3 (6%)	0	0	1 (4%)	0	3 (12%)	2 (8%)	0
Acute kidney injury	1 (2%)	0	1 (2%)	0	0	1 (4%)	1 (4%)	0	0
Hypocalcaemia	1 (2%)	1 (2%)	0	1 (4%)	0	0	0	1 (4%)	0
Systemic inflammatory syndrome	0	1 (2%)	0	0	0	0	0	1 (4%)	0
Myocarditis	0	1 (2%)	0	0	1 (4%)	0	0	0	0
Pancreatitis	0	1 (2%)	0	0	0	0	0	1 (4%)	0
Syncope	0	1 (2%)	0	0	1 (4%)	0	0	0	0

Treatment-related adverse events are graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.0. The table shows grade 1–2 adverse events occurring in at least 10% of patients and all grade 3 and 4 adverse events. The number in each column reflects the number of patients with highest grade adverse events within that adverse event category. SBRT=stereotactic body radiotherapy.

Table 3: **Treatment-related adverse events**

therapy remains a substantial clinical challenge. Platinum-based chemotherapy generally only offers transient responses in Merkel cell carcinoma[23] and targeted therapies have not been successful.[24,25] As Merkel cell carcinoma is a relatively rare tumour type, we adopted a randomised study design with two experimental groups, which allowed us to evaluate the efficacy of dual checkpoint inhibitor blockade targeting PD-1 and CTLA4, as well as the potential role for subablative immunogenic SBRT, in both ICI-naive patients and patients for whom pembrolizumab or avelumab had previously failed.

To our knowledge, our study is the first to evaluate the use of dual checkpoint-inhibitor blockade as first-line therapy in advanced Merkel cell carcinoma. The results to date suggest remarkable clinical activity of combined PD-1 and CTLA4 blockade in ICI-naive patients with Merkel cell carcinoma. Although combined nivolumab and ipilimumab was not directly compared with anti-PD-1 and PD-L1 monotherapy, the observed ORR in 22 of 22 patients (100% [95% CI 82–100), with complete response in 9 (41%) of 22 patients in ICI-naive patients, is substantially higher than would be expected with monotherapy.[4,7] Further, combined nivolumab and ipilimumab showed substantial durability of response in the ICI-naive cohort. However, given emerging reports of high rates of Merkel cell carcinoma relapse following ICI discontinuation,[26] longer follow-up will be needed to assess response durability for patients treated on this trial, particularly after treatment discontinuation.

Relapsed or refractory disease following anti-PD-1 and PD-L1 monotherapy remains a clinical challenge. Although far less robust than in the ICI-naive population,

our results support clinically meaningful activity in the ICI-relapsed or ICI-refractory population, as has been suggested by retrospective reports published since 2019,[27,28] but contrasts with one retrospective report that showed zero objective responses in 13 treated patients.[29] In this latter study, it is notable that the majority of treated patients had poor performance status (ECOG >1), presumably due to advanced disease, and five (38%) of 13 had received cytotoxic chemotherapy between previous ICI and combined nivolumab and ipilimumab. No information is available on the number of patients who had received cytotoxic chemotherapy before first-line ICI. In contrast, in our study, all patients had good performance status and only one (4%) of 26 had received chemotherapy in between previous ICI treatment and enrolment to our study. Four (15%) of 26 patients had received chemotherapy before first-line ICI. Taken in context of these previous reports, our study results suggest that the nivolumab and ipilimumab combination has the highest chance of success when implemented early in the disease process for advanced Merkel cell carcinoma, before single-agent-ICI failure and before cytotoxic chemotherapy use.

The concept of SBRT as an in-situ tumour vaccine harnessing an immunogenic effect has actively been investigated since 2009 with some positive findings,[13,14] but also with negative findings.[30] In our study, the addition of SBRT did not improve ORR in comparison with combined nivolumab and ipilimumab alone. Given the extremely high ORR among ICI-naive patients in both groups, it would have been difficult to see any additive or synergistic benefit of SBRT, if it existed. Conversely, in the previous-ICI cohort, any immunogenic effect of SBRT could have been too modest to affect clinical outcomes in the face of a heavily dysfunctional tumour-immune microenvironment.[31] Although not significant, ORR was numerically lower in the previous-ICI group that received SBRT (three [21%] of 14 patients [95% CI 6–51] in group B) as compared with the group that did not (five [42%] of 12 patients [16–71] in group A). Given the small patient sample size, our study was not sufficiently powered to address whether SBRT has a subtle detrimental effect on combined nivolumab and ipilimumab efficacy following previous ICI, and further studies would be required to answer this question. Regardless, our data does not support routinely incorporating SBRT with combination ICI therapy in advanced Merkel cell carcinoma unless indicated for palliative reasons. In cases in which SBRT is considered for palliation, our study shows that 24 Gy delivered in three fractions can be safely administered in combination with combined nivolumab and ipilimumab. Additionally, the excellent local control observed suggests a de-escalated radiation dose might be sufficient for local control in Merkel cell carcinoma. This possibility warrants further investigation, particularly for patients with early stage Merkel cell carcinoma who routinely receive radiation doses over 50 Gy, as has been suggested by a previous report.[32]

Subgroup analysis of baseline PD-L1 expression or Merkel cell polyomavirus status did not reveal any association with clinical response consistent with prior studies with anti-PD1 or PDL1 monotherapy (appendix p 2). Interestingly, subgroup analysis of the previous-ICI cohort revealed numerically higher ORR among patients who were previously exposed to PD-L1 blockade versus PD-1 blockade (five [45%] of 11 patients [95% CI 18–75] *vs* three [21%] of 14 patients [6–51]; appendix p 3), although this difference did not translate into survival outcome (appendix p 4). Although our study does not have the statistical power to conclude whether there is a true difference in the efficacy of combined nivolumab and ipilimumab as a salvage regimen following first-line failure after anti-PD-1 therapy versus anti-PD-L1 therapy, further investigation is warranted to determine whether a non-overlapping mechanism of PD-1 versus PD-L1 blockade might lead to an altered therapeutic response to combined nivolumab and ipilimumab.

The combined nivolumab and ipilimumab regimen used in our trial showed an expected safety profile, as compared with larger studies in other disease sites using the same regimen. Because most patients with Merkel cell carcinoma are older, a low dose of ipilimumab (1 mg/kg every 6 weeks) was selected for this study. Grade 3 and 4 treatment-related toxicities were observed in 36% of the patients enrolled, similar to that observed with phase 3 studies in non-small cell lung cancer (CheckMate-227) and malignant mesothelioma (CheckMate-743) using the same dose and schedule of combined nivolumab and ipilimumab,[10,33] and substantially lower than that observed with higher doses of ipilimumab in combination with anti-PD-1 and PD-L1.[34] Whether or not a regimen including a higher dose or greater frequency of administration of ipilimumab than that used in this study would have greater efficacy in the refractory disease setting merits further evaluation.

This study does have limitations. This is a phase 2 study from two centres with a small patient sample size. Additionally, this was a non-registrational trial and independent assessment was not done. However, Merkel cell carcinoma is one of the rarest malignancies affecting the older population, with the majority of cases affecting patients older than 65 years who often have substantial comorbidities, which renders large, phase 3 studies difficult.

Despite these limitations, our results suggest that first-line therapy with the combination therapy of nivolumab and ipilimumab in patients with recurrent or metastatic Merkel cell carcinoma is effective and durable with a manageable safety profile. The nivolumab and ipilimumab combination therapy has also shown clinical activity in patients for whom anti-PD-1 and PD-L1 monotherapy has previously failed, albeit with a far lower

response than in the first-line setting. With further validation from followup studies, combined nivolumab and ipilimumab could be considered in the first-line and salvage setting.

Contributors

The principal investigators (SK) and co-investigator (JR) were responsible for the design of the study. SK and DB were responsible for the oversight of the study. The manuscript was written and prepared by the authors, who adhered to the study protocol to report complete and accurate data. The Moffitt Cancer Center was responsible for centralising and maintaining the collected data. SK, EW, DB, ZE, CV, JR, JJC, AT, JM, KK, RW, NIK, and ASB accrued patients to the study. SK, RT, MM, KD, CL, D-TC, LM, BAP, and ASB collected and assembled the data. Authors involved in exploratory biomarker studies only had de-identified information so as to avoid Health Insurance Portability and Accountability Act violation. Otherwise, all authors had full access to all the data in the study, analysed and interpreted the data, wrote the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

SK reports research support from Bristol Myers Squibb for the submitted work and research support from Bristol Myers Squibb and AstraZeneca outside the submitted work. EW reports being a member of the advisory board for Viewray, Varian, Alphatau, Castle Biosciences, and Teiko outside the submitted work. ZE reports being a member of the advisory board for Array, Pfizer, OncoSec, Regeneron, Genentech, Novartis, Natera, and Eisai outside the submitted work and research support for Novartis, Pfizer, and Boehringer-Ingelheim outside the submitted work. JJC reports research support for Varian and Galera outside the submitted work. AT reports research support for Bristol Myers Squibb, Genentech-Roche, Regeneron, Sanofi-Genzyme, Nektar, Clinigen, Merck, Acrotech, Pfizer, Checkmate, and OncoSec outside the submitted work and personal fees from Bristol Myers Squibb, Merck, Eisai, Instil Bio, Clinigen, Regeneron, Sanofi-Genzyme, Novartis, Partner Therapeutics, Genentech/Roche, and BioNTech outside the submitted work. JM reports research support from Microba, Jackson Laboratories, Merck, and Morphogenesis outside the submitted work. BAP reports being a member of the advisory board for Bristol Myers Squibb, AstraZeneca, and G1 therapeutics outside the submitted work. VKS reports research support from Neogene and Turnstone outside the submitted work and being a member of the advisory board for Bristol Myers Squibb, Eisai, Iovance, Merck, Novartis, Regeneron, and Statking outside the submitted work. NIK reports being a member of the advisory board for Bristol Myers-Squibb, Regeneron, Merck, Jounce Therapeutics, Iovance Biotherapeutics, Genzyme, Novartis, Castle Biosciences, Nektar, and Instill Bio outside the submitted work; being a member of the steering or scientific committee for Nektar, Regeneron, Replimune, Bristol Myers-Squibb, and National Comprehensive Cancer Network via Pfizer outside the submitted work; being on the data safety monitoring committee for AstraZeneca and Incyte outside the submitted work; research support to his institution outside the submitted work from Bristol Myers-Squibb, Merck, Celgene, Regeneron, Replimune, Novartis, HUYA Bioscience, and GlaxoSmithKline); and common stock from Bellicum, Amarin, Asensus Surgical outside the submitted work. ASB reports being a member of the advisory board for Deciphera and Bayer outside the submitted work. All other authors have no interests to declare.

Data sharing

Individual participant data will be available, beginning 3 months and ending 5 years following article publication, to the researchers who provide a methodologically sound proposal to achieve aims in the approved proposal. All of the individual participant data collected during the trial will be shared after deidentification. The study protocol and statistical analysis plan will also be available. Proposals should be directed to sungjune.kim@moffitt.org. To gain access, data requestors will need to sign a data access agreement.

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