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Single-arm, open-label phase 2 trial of pembrolizumab in patients with leptomeningeal carcinomatosis

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An increasing fraction of patients with metastatic cancer develop leptomeningeal dissemination of disease (LMD), and survival is dismal[1–3]. We conducted a single-arm, phase 2 study of pembrolizumab in patients with solid tumor malignancies and LMD (NCT02886585). Patients received 200 mg of pembrolizumab intravenously every 3 weeks until definitive progression or unacceptable toxicity. The primary endpoint was rate of overall survival at 3 months (OS3). Secondary objectives included toxicity, response rate and time to intracranial or extracranial disease progression. A Simon two-stage design was used to compare a null hypothesis OS3 of 18% against an alternative of 43%. Twenty patients—17 with breast cancer, two with lung cancer and one with ovarian cancer—were enrolled into the pre-specified evaluation group having received at least one dose of pembrolizumab. The median follow-up of surviving patients was 6.3 months (range, 2.2–12.5 months). The percentage of patients who experienced one (or more) grade 3 or higher adverse events at least possibly related to treatment was 40%, the most frequent being hyperglycemia ($n = 6$), nausea ($n = 7$) and vomiting ($n = 7$). The study met the primary endpoint, as 12 of 20 (OS3, 0.60; 90% confidence interval, 0.39–0.78) patients were alive at 3 months after enrollment. Pembrolizumab is safe and feasible and displays promising activity in patients with LMD. Further investigations are needed to identify which patients with LMD can benefit from pembrolizumab.

Leptomeningeal carcinomatosis, otherwise known as LMD, represents the spread of cancer to the leptomeninges and occurs in approximately 5–10% of patients with solid tumors[1,2]. Diverse solid tumors can metastasize to the leptomeninges, although breast and lung cancers are the most common. As patients with cancer are surviving longer with improved systemic therapies and diagnostic imaging techniques, LMD is being diagnosed more frequently. Patients can present with a number of neurologic signs and symptoms, including increased intracranial pressure, cranial nerve palsies, seizures, encephalopathy, radiculopathies and cauda equina syndrome[1]. Historically, patient cohorts with leptomeningeal metastases have a poor median survival—approximately 3–7 weeks in several series[3–13].

Current treatment of LMD involves radiation to symptomatic sites of the central nervous system (CNS) and to sites of bulky disease seen on imaging studies, with consideration of intrathecal chemotherapy and/or systemic therapy[1,2]. Overall, despite the existence of published guidelines regarding the management of LMD, management varies widely, and there is no broadly accepted standard of care. While survival might be extended in some patients with radiation therapy and/or intrathecal chemotherapy, outcomes remain unsatisfactory for most patients. Whole-brain radiation therapy (WBRT) and/or craniospinal radiation are associated with myelosuppression as well as other CNS toxicities, with no definitive data to suggest an improvement in OS[3,14]. Systemic chemotherapy has limited access to the cerebrospinal fluid (CSF). Although chemotherapy administered intrathecally treats tumor cells in the CSF, effectiveness is limited and treatment-related toxicities, such as chemical meningitis, vomiting and severe headaches, are common[4,15]. For example, in a randomized trial comparing intrathecal DepoCyt versus intrathecal methotrexate, median OS was only 105 d and 78 d, respectively. DepoCyt has since been discontinued. Another option—intrathecal methotrexate administered twice weekly—is associated with significant toxicities (including 19% with chemical meningitis)[15]. Improved treatments are desperately needed to improve survival outcomes in patients with LMD.

Great strides in oncology have been made by targeting key regulators of immune activation and effector function, including monoclonal antibodies against cytotoxic T-lymphocyte-associated protein 4 (CTLA4), programmed cell death receptor 1 (PD-1) and its ligand (PD-L1). Furthermore, many of these checkpoint inhibitors have shown high response rates in parenchymal brain metastases from lung cancer and melanoma[16–19], suggesting that the immune response can overcome the anatomic barriers to effective systemic anti-cancer therapies in the CNS. However, the role of these inhibitors in leptomeningeal carcinomatosis has not been

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Table 1 | Patient demographics and baseline disease characteristics

	n
Sex – no. (%)	
Female	20 (100)
Male	0
Median age, years (range)	51.5 (33–64)
Initial primary tumor diagnosis – no. (%)	
Breast	17 (85)
HR^+ $HER2^+$	3
HR^+ $HER2^-$	7
HR^- $HER2^+$	3
Triple-negative	3
Unknown	1
Non-small cell lung cancer not otherwise specified	1 (5)
Small cell carcinoma of lung	1 (5)
Ovarian	1 (5)
ECOG performance status – no. (%)	
0	6 (30)
1	13 (65)
2	1 (5)
Estrogen receptor status – no. (%)	
Positive	11 (55)
Negative	6 (30)
Not applicable	3 (15)
Progesterone receptor status – no. (%)	
Positive	9 (45)
Negative	8 (40)
Not applicable	3 (15)
Hormone receptor status – no. (%)	11 (55)
Positive	
Negative	6 (30)
Not applicable	3 (15)
HER2 status – no. (%)	
Negative	11 (55)
Not applicable	2 (10)
Positive	7 (35)
Time since initial diagnosis of primary tumor, months (range)	39.5 (3–202)
Time since LMD diagnosis and enrollment, months (range)	1.9 (0.3–23.6)
Extracranial disease – no. (%)	15 (75)
Bone	10 (50)
Liver	3 (15)
Lung	3 (15)
Lymph node	11 (55)
Skin	1 (5)
Adnexal	1 (5)
Pancreas	1 (5)
Chest wall	1 (5)
Visceral	1 (5)
Prior therapy – no. (%)	
Radiation	18 (90)
Intracranial radiation	14 (70)
WBRT	9 (45)
Surgery	19 (95)
Prior systemic therapy	20 (100)
On dexamethasone at enrollment – no. (%)	6 (30)

Table 2 | Efficacy

	n	%
Rate of OS at 3 months		
Alive at 3 months	12	60
Not alive at 3 months	8	40
Best response iRANO		
Stable disease[a]	11	55.0
Progressive disease	5	25.0
Not evaluable[b]	4	20.0
Best response RECIST		
Stable disease[a]	10	50.0
Progressive disease	1	5.0
Not evaluable[b]	9	45.0

[a]Includes stable disease or non-complete response/non-progressive disease in cases where there is no detected disease at baseline or follow-up exams. [b]Includes cases of restaging scans not obtained.

adequately explored owing to the historical pattern of systematic exclusion of this patient population in clinical trials.

Results

Trial. We conducted a phase 2 study of pembrolizumab in patients with CNS metastases (NCT02886585). Cohorts A, B and D included patients with parenchymal brain metastases and were analyzed separately. Cohort C, reported herein, included patients with leptomeningeal carcinomatosis.

Patients. From October 13, 2016, to April 25, 2018, a total of 22 patients were consented and enrolled in Cohort C of the study (Extended Data Fig. 1); of these patients, two did not receive study therapy owing to subsequent patient decision not to pursue therapy ($n=1$) or clinical deterioration ($n=1$). The analytic cohort consisted of 20 patients who were enrolled and had received at least one dose of pembrolizumab. All patients in the analytic cohort were female, with a median age at the time of study enrollment of 51.5 years (range, 33–64 years; Table 1). Ninety-five percent of patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Initial diagnosis of breast cancer occurred in 85% of patients ($n=17$), six of whom had human epidermal growth factor receptor 2 (HER2)-positive disease. If only the subset of patients with breast cancer is considered, the rates of estrogen receptor (ER), progesterone receptor (PR) and hormone receptor (HR) positivity were 65% (11 of 17), 53% (9 of 17) and 65% (11 of 17), respectively, and the rate of triple-negative breast cancer was 18% (3 of 17). Two patients remained on trastuzumab concurrently with pembrolizumab, and two patients remained on endocrine therapy (letrozole or fulvestrant) concurrently with pembrolizumab. No patients had a known *BRAF*, *EGFR* or *ALK* mutation in the overall cohort. The median time between initial cancer diagnosis and study enrollment was 39.5 months (range, 3–202 months). Seventy percent of patients had coexisting extracranial disease, the most common sites being lymph node ($n=11$) and bone ($n=10$). Patients were heavily pre-treated, with all patients having received prior systemic therapy, with a mean of five prior systemic therapies (s.d., 3; range, 1–11). Ninety percent of patients received prior radiation therapy (70% to a CNS site), and 95% of patients received prior surgery (Table 1). Of the 18 patients who reported prior radiation therapy, six had undergone radiation both before and after LMD diagnosis, 11 after LMD diagnosis only and one before LMD diagnosis only. The median time between the last brain-directed radiation therapy and enrollment was 3.2 months (range, 0.23–21.9 months).

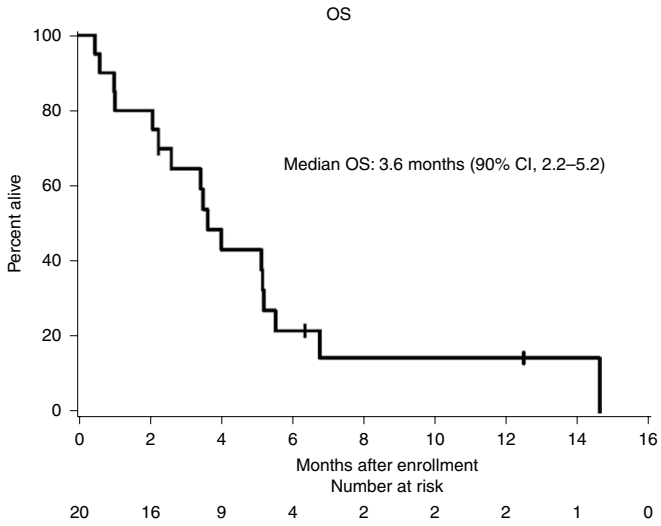

Fig. 1 | Kaplan-Meier curve in all patients with leptomeningeal disease treated with pembrolizumab ($n=20$).

Efficacy. Twelve patients (60%) were alive at 3 months after enrollment (OS3). Per the pre-specified criteria, the requirement for a successful primary endpoint under the study design was six or more patients alive at 3 months. Therefore, the study met its primary endpoint (Table 2).

The proportion of patients with OS3 was 0.60 (12 of 20; 90% exact confidence interval (CI), 0.39–0.78). Median survival was 3.6 months (90% CI, 2.2–5.2 months) (Fig. 1 and Extended Data Fig. 2). For the 17 patients with breast cancer, the rate of ER positivity (or HR positivity) of patients alive at 3 months was 60% (6 of 10) compared to 57% (4 of 7) who did not survive to 3 months (Fisher's exact $P=0.64$). Rates of PR positivity were 60% (6 of 10) and 29% (2 of 7) for patients who were alive at 3 months and not alive at 3 months, respectively (Fisher's exact $P=0.23$). Based on these data, there does not appear to be a clearcut relationship between outcome and ER/PR status in patients with a primary diagnosis of breast cancer. Similarly, there does not appear to be a relationship between outcome and HER2 status. Median OS for patients who were HER2 positive was 4.4 months (90% CI, 1–6.8 months) and 3.4 months (90% CI, 2.1–4.0 months) for HER2 negative (log-rank $P = 0.65$). The median OS in the group of patients who received dexamethasone at enrollment was 2.4 months (90% CI, 0.6–3.5); the median OS of the patients who did not receive dexamethasone was 5.1 months (90% CI, 3.4–5.5), with a log-rank P value of 0.32.

In exploratory analyses, PD-L1 expression was measured from archival intracranial or extracranial tissue using immunohistochemical analysis. The median OS for patients who had PD-L1-positive disease (more than 0% of cells expressing PD-L1) was 3.5 months (95% CI, 0.6–5.2 months) compared to 3.1 months (95% CI, 2.1–5.2 months) for patients with PD-L1-negative disease.

For CNS disease, responses were assessed every 6 weeks with magnetic resonance imaging (MRI) using Immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria, with 11 of the 20 patients showing stable disease in the CNS as the best response (Table 2). For extracranial disease, responses were assessed every 6 weeks with computed tomography (CT) of the chest, abdomen and pelvis using Response Evaluation Criteria in Solid Tumors 1.1 (RECIST), with 10 of the 20 patients showing stable disease extracranially as the best response. Of the six patients with progressive disease by iRANO criteria, the median intracranial progression-free survival was 2.6 months (90% CI, 1.1–5.2 months). Of the five patients with documented progressive extracranial disease by RECIST, the median extracranial progression-free survival was 3.6 months (90% CI, 2.1–5.2 months). Of the 18 patients for whom we had data at the time of death, ten had CNS-only progression, three had extracranial-only progression and five had progression both in the CNS and extracranially.

We evaluated CSF cell counts and protein collected as part of clinical care before and during treatment with pembrolizumab. For the 11 patients with pre-treatment lymphocyte data from CSF available, patients with an OS of more than 3 months had higher lymphocyte percentages at pre-treatment, although this comparison was not statistically significant (median, 42.0% versus 19.0%; exact Wilcoxon rank-sum $P=0.27$). In the subset of 13 patients with pre-treatment and week-6 measurements of protein from the CSF collected clinically, there was a statistically significant increase relative to pre-treatment (median fold change = 1.6; range, 0.6–6.0; Wilcoxon signed-rank $P=0.003$). In exploratory analyses, we also performed single-cell sequencing profiling from CSF collected before and after pembrolizumab (analysis to be published separately).

Adverse events. Nineteen of 20 patients had one or more adverse events (AEs) that were considered to be at least possibly related to treatment (Table 3 and Extended Data Figs. 3 and 4). Eight patients had one or more grade 3 or higher AEs that were at least possibly related to treatment. The observed percentage was 40% (90% exact CI, 22–61%). The most frequently occurring AEs deemed at least possibly related to protocol therapy were hyperglycemia ($n=6$), nausea ($n=7$) and vomiting ($n=7$).

Discussion

LMD continues to have an extremely poor prognosis with few treatment options[3,4,20]. As LMD tends to be a late manifestation of cancer, most patients with LMD have treatment-resistant disease by the time their disease spreads to the leptomeninges. Moreover, the vast majority of trials routinely exclude patients with LMD, thus limiting the ability to assess the efficacy of newer agents in LMD. In this phase 2 study, we demonstrated that treatment with single-agent PD-1 inhibitor was safe and associated with a 3-month OS of 60% in a heavily pre-treated population of patients with LMD.

We chose a stringent test of OS as the primary endpoint, selecting a high survival threshold at a 3-month landmark, a timepoint that is nearly double the poor median survival observed in this population in historical series[3–8,10–12]. We eschewed surrogate endpoints given the challenges with assessing LMD response to treatment pathologically, clinically and radiographically[3]. Lumbar punctures have demonstrably high false-negative rates[3]. Radiographically, in the absence of parenchymal brain metastases, precise measurements of tumor burden are difficult given the nature of LMD, manifesting as diffuse and thin contrast enhancement along the brain sulci and gyri. As a secondary endpoint, we evaluated the modern iRANO criteria[21] to assess responses in the CNS and showed that 55% of patients had stable disease in the CNS as their best response.

One possible explanation for improved responses compared to historical controls is the potential for the immune system to access the CSF compartment, which has traditionally been considered to be a sanctuary site. However, the vast majority of patients enrolled in this study had breast cancer, a population in which single-agent checkpoint blockade has demonstrated limited activity at best. A recent study in advanced triple-negative breast cancer showed that atezolizumab and nab-paclitaxel prolonged progression-free survival and OS in patients with PD-L1-positive tumors; however, this study excluded patients with LMD[22]. In the JAVELIN trial, the likelihood of extracranial response or prolonged clinical benefit to single-agent checkpoint blockade in patients with ER-positive and HER2-negative breast cancer or HER2-positive breast cancer was less than 5%[23]. In exploratory analyses, there did not appear to be a relationship between survival outcome and HR or HER2 status, although our cohort size was small and therefore might have been

Table 3 | AEs at least possibly related to treatment (includes all grade 3 and 4 toxicities, immune-related AEs and any toxicities that occurred at least two times)

	01-Mild	02-Moderate	03-Severe	04-Life Threatening
	n	*n*	*n*	*n*
Toxicity description CTCAE v4.0	—	—	—	—
Vomiting	6	—	1	—
Nausea	3	2	2	—
Hyperglycemia	6	—	—	—
Constipation	5	—	—	—
Headache	2	—	3	—
Fatigue	4	1	—	—
Alanine aminotransferase increased[a]	1	3	—	—
Pericarditis[a]	—	1	—	—
Aspartate aminotransferase increased[a]	2	—	2	—
Anorexia	3	—	—	—
Dizziness	2	1	—	—
Abdominal pain	1	1	—	—
Colitis[a]	—	2	—	—
Alkaline phosphatase increased[a]	2	—	—	—
Dry skin	2	—	—	—
Hypokalemia	2	—	—	—
Weight loss	2	—	—	—
Bone pain	1	—	1	—
Muscle weakness lower limb	—	—	1	—
Lymphocyte count decreased	—	—	1	—
Platelet count decreased	—	—	1	—
Somnolence	—	—	1	—
Syncope	—	—	1	—
Pneumonitis[a]	—	1	—	—
Respiratory failure	—	—	—	—

[a]Immune-related adverse events.

underpowered for this specific analysis (the two patients surviving 1 year or more were a patient with breast cancer who lived 14.6 months and a patient with lung cancer who was censored for OS at 12.5 months). A high frequency of PD-L1 expression has been reported in breast cancer brain metastases, irrespective of ER or HER2 status, and this raises the possibility that sensitivity to immune checkpoint blockade might be different in CNS versus extracranial sites[24]. It is also possible that prior rounds of treatment, including chemotherapy and/or radiation, result in a disease state that could be more responsive to immunotherapy. Further study will be required to determine whether these hypotheses can be supported by clinical data.

A common question arising with the study of immunotherapy in CNS metastatic disease is whether steroids abrogate the efficacy of checkpoint blockade and therefore should be curtailed. In a phase 2 trial of ipilimumab in patients with parenchymal brain metastases, asymptomatic patients not on steroids had a higher disease control rate than symptomatic patients on steroids[17]. In our trial, more than 50% of patients received dexamethasone at some time during the course of their treatment with pembrolizumab, with 30% of the patients on low-dose dexamethasone at the time of enrollment. Although we observed a numerically improved OS in patients not on dexamethasone at enrollment, this difference was not statistically significant ($P=0.32$). Given the uncontrolled administration of steroids in these trials, it is possible that the clinical requirement for more steroids could be associated with a more aggressive disease course and thus could be associated with a poorer response independent of the immunosuppressive effects of corticosteroids. A larger study in patients with LMD will allow us to more definitely answer this important clinical question.

Notably, the toxicity profile in this patient population, often considered too frail for further aggressive treatment, was largely consistent with the known AEs of pembrolizumab. Most grade 3 and 4 possibly-related side effects were not immune-related AEs and included headaches in three patients. This toxicity profile is an important consideration given that most patients enrolled in this study had an ECOG performance status of 1 or higher. Of note, there were no life-threatening nervous system toxicities related to treatment. By comparison, other treatments used for LMD carry significant toxicity. Intrathecal chemotherapy has high rates of neurotoxicity, with 8–24% of patients developing aseptic meningitis[25]. Also, most intrathecal chemotherapy is administered at least once per week, which can be challenging for patients with a poor performance status and limited survival; in contrast, pembrolizumab is a short infusion administered every 3 weeks. Systemic chemotherapy, especially in combination with radiation, can have substantial side effects[3].

Our study had several limitations. First, although open to patients with any solid tumor, most of the enrolled patients had breast cancer. Therefore, the results of the study cannot be generalized to other histologies at this time. Second, documenting response in LMD is challenging, and thus surrogate endpoints such as response rate and progression-free survival, which are commonly used to measure efficacy in small data sets, were not feasible. Thus, OS was selected at a stringent level to be our efficacy endpoint; nevertheless, the historical and contemporary data around OS in this patient population was highly variable[26–28]. Given that all patients in this study were heavily pre-treated and several had progressed after WBRT before going on study, our patient population might not be representative of other prior clinical studies, which enrolled newly diagnosed leptomeningeal carcinomatosis with better performance status. Predictive biomarkers of response remain to be further explored.

In conclusion, this study represents the first prospective clinical trial to evaluate the efficacy and safety of immune checkpoint inhibitors specifically in patients with LMD. The trial met its primary efficacy endpoint, suggesting that pembrolizumab might be a promising treatment for patients with otherwise limited therapeutic options. Of the 18 patients for whom we had data at the time of death, 15 of 18 (83%) had CNS progression. More studies are needed to understand why patients can manifest heterogeneous responses in the CNS and extracranially. Most importantly, we showed that such treatments in this patient population are safe and not associated with excessive neurological or other toxicity. Although the data presented herein are encouraging, our conclusions are necessarily tempered by the small study size with a heterogeneous patient population. Ultimately, combinations of pembrolizumab with other therapies warrant further evaluation in LMD, including combinations with radiation therapy or chemotherapy.

Online content

Any methods, additional references, Nature Research reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information; details of author contributions and competing interests; and statements of data and code availability are available at https://doi.org/10.1038/s41591-020-0918-0.

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Methods

Study design and patients. *Study oversight.* The study (Clinicaltrials.gov identifier NCT02886585) was designed by the principal investigators and conducted in accordance with the provision of the Declaration of Helsinki and Good Clinical Practice guidelines (Supplementary Information). The Dana-Farber/Harvard Cancer Center institutional review board approved the protocol. Funding was provided by the Melanoma Research Alliance, Merck and Massachusetts General Hospital.

Patients. Eligible patients had histologically confirmed disease from any solid tumor, had an ECOG performance status of 2 or lower, had normal organ and marrow function, were on a stable dose of dexamethasone of 2 mg or lower for 7 d before the initiation of treatment and had leptomeningeal meningitis as defined by positive cytology. There were no specific radiographic criteria for eligibility. Patients who had received prior CNS-directed treatment, including prior treatment for leptomeningeal meningitis, were eligible. Patients were excluded if they had a diagnosis of immunodeficiency or active autoimmune disease, had a known history of active non-infectious pneumonitis, received prior treatment with a PD-1 or PD-L1 inhibitor or had received systemic immunosuppressive treatments aside from corticosteroids within 3 months of study drug. Written informed consent was obtained for all participants.

Study design, treatment and endpoints. This was Cohort C of an ongoing phase 2 study of pembrolizumab in patients with CNS metastases (NCT02886585). Cohorts A, B and D includes patients with parenchymal brain metastases and are being analyzed and reported separately. Cohort C includes patients with solid tumors with leptomeningeal carcinomatosis as defined by positive cytology. Separate analyses of each cohort were pre-specified. Pembrolizumab was administered intravenously at 200 mg every 3 weeks until disease progression, death or unacceptable toxicity. A brain MRI and CT of the chest, abdomen and pelvis were obtained every 6 weeks for restaging. The primary endpoint was the rate of OS3. Any patient whose vital status at 3 months could not be determined was counted as having died for the primary endpoint analysis. Secondary objectives included toxicity, CNS response rate using iRANO[21], extracranial response rate using RECIST 1.1, time to the first occurrence of extracranial disease progression or death from any cause and time to the first occurrence of intracranial disease progression or death from any cause. All radiographic images were reviewed centrally by radiologists through the Tumor Imaging Metrics Core using these pre-specified imaging criteria.

Statistical analysis. With a historical median OS of approximately 5–6 weeks in this patient population (as determined from previous reports in the literature[3–13] and our institutional database), a Simon two-stage design was used to compare a null hypothesis that OS3 would be 18% against an alternative of 43% (Life Sciences Reporting Summary). Ten patients were to be enrolled in the first stage. If zero or one patients were alive at 3 months, the trial would stop early owing to futility. If two or more patients were alive at 3 months, an additional eight patients would be enrolled. If at least six patients of the total of 18 patients were alive at 3 months, the treatment would be considered promising in the cohort. This design had a type I error of 9% (target, 10%) and a power of 85%. If the null hypothesis were true, then the probability would be 0.45 of stopping at the end of the first stage. Survival status was monitored carefully during the first stage of the Simon design. On March 1, 2017, a second patient in the first stage was alive at 3 months; therefore, enrollment continued without pause into the second stage.

The primary endpoint, OS3, and CNS and extracranial response rates are summarized with 90% exact binomial CIs. Toxicities that were new or worsening relative to baseline are summarized according to the worst grade occurring for each patient. The distribution of OS is presented using the Kaplan–Meier method with 90% CIs estimated using log(-log) methods.

Reporting Summary. Further information on research design is available in the Nature Research Reporting Summary linked to this article.

Data availability

Any requests for raw and analyzed data will be reviewed by the Dana-Farber/Harvard Cancer Center institutional review board. Patient-related data not included in the paper were generated as part of a clinical trial and are subject to patient confidentiality. Any data and materials (for example, tissue samples or imaging data) that can be shared will need approval from the Dana-Farber/Harvard Cancer Center institutional review board and a Material Transfer Agreement in place. All data shared will be de-identified.

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Author contributions

P.K.B., R.J.S. and D.P.C. conceived the study. P.K.B. wrote the protocol with input from R.J.S., D.P.C., S.L.C., A.G.-H., T.T.B., E.R.G. and K.O. E.Q.L., J.V.C., S.M.T., N.U.L., N.W., U.C., M.D.W., C.A.-B., I.K., M.K.M., L.N., J.D., D.A.F., B.V.N., T.T.B., H.A.S., E.R.G., B.M., P.K.B., R.J.S., D.P.C., K.O. and D.L. supported the clinical trial, including recruitment and/or management of patients in the trial. A.G.-H. performed the statistical analysis. B.S., N.G., N.N., A.K., J.L.M., M.D.W., M.S.B. and M.S. helped collect data and samples. E.R.G. was the imaging chair of the study. P.K.B., D.P.C. and R.J.S. wrote the manuscript. All authors interpreted the data, reviewed the manuscript and approved the final version.

Competing interests

P.K.B. has consulted for Tesaro, Angiochem, Genentech-Roche, ElevateBio and Eli Lilly, has received institutional research funding (to Massachusetts General Hospital) from Merck, Eli Lilly, BMS and Pfizer and has received honoraria from Merck and Genentech-Roche. J.C. has received consulting fees from Sanofi-Genzyme and BMS. D.P.C. has consulted for Eli Lilly and Boston Pharmaceuticals and has received travel and speaking fees from Merck. S.M.T. receives institutional research funding from Novartis, Genentech, Eli Lilly, Pfizer, Merck, Exelixis, Eisai, Bristol Meyers Squibb, AstraZeneca, Cyclacel, Immunomedics, Odenate and Nektar. S.M.T. has served as an advisor and consultant to Novartis, Eli Lilly, Pfizer, Merck, AstraZeneca, Eisai, Puma, Genentech, Immunomedics, Nektar, Tesaro, Daiichi Sankyo, Athenex, Sanofi, Bristol Meyers Squibb and Nanostring. N.U.L. has received institutional research funding from Seattle Genetics, Genentech, Merck and Pfizer. N.U.L. has also served on an advistory board or consulted for PUMA Biotechnology, Seattle Genetics and Daichii Sankyo. R.J.S. has received research funding from Amgen and Merck and has served as a paid consultant and/or been on an advisory board for Array BioPharma, Amgen, Asan Biosciences, BMS, Compugen, Genentech, Merck, Novartis and Replimmune. E.Q.L. has received royalties from Wolters Kluwers (UpToDate, Inc) and has consulted for Eli Lilly. B.M. has received institutional research funding from PUMA Biotechnology. D.A.F. is an Eli Lilly shareholder. I.K. has received personal fees for being a member of a Merck DSMC, has received research funding from Genentech and Pfizer and has served as a paid consultant and/or been on an advisory board for Genentech, Bristol Meyers Squibb, Daiichi/Sankyo, Macrogenics and AstraZeneca. T.T.B. is on the Scientific Advisory Board for Genomicare. M.D.W. is a consultant at Boston Pharmaceuticals. Dana-Farber Cancer Institute has a financial interest in pembrolizumab and has taken steps to manage any actual or potential conflict of interest created by this financial interest, which was described in the information sheet available to all participants in this study.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s41591-020-0918-0.

Supplementary information is available for this paper at https://doi.org/10.1038/s41591-020-0918-0.

Correspondence and requests for materials should be addressed to P.K.B.

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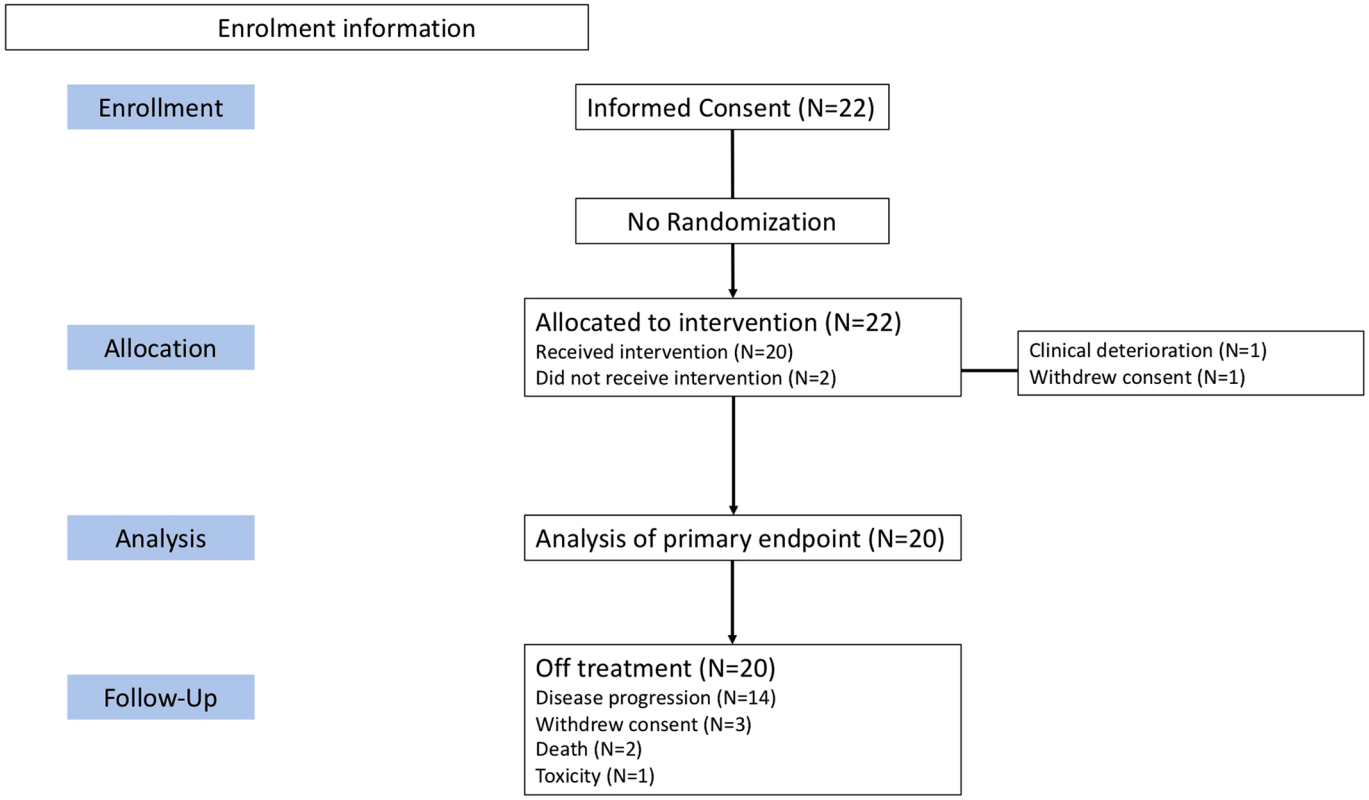

Extended Data Fig. 1 | Enrolment information. A total of 22 patients with leptomeningeal carcinomatosis were consented and enrolled to the study between October 2016 to April 2018.

Characteristics of patients alive at three months									
Case number	*OS Months*	*Primary Diagnosis*	*ER Status*	*PR Status*	*HER-2 Status*	*Prior CNS radiation*	*ECOG PS*	*Corticosteroids at baseline*	*Visible on Imaging*
3	5.2	Breast	Neg	Neg	Pos	WBRT	0	No	Yes
6	6.8	Breast	Pos	Pos	Pos	Spinal cord	1	No	No
24	5.5	Breast	Pos	Pos	Neg	WBRT	1	No	No
33	6.3	Breast	Neg	Neg	Pos	WBRT	2	No	Yes
37	4.0	Breast	Neg	Neg	Neg	Spinal cord	1	No	No
42	3.5	Breast	Pos	Pos	Neg	Spinal cord	0	Yes	No
45	5.1	NSCLC	-	-	-	SRS	1	No	No
46	14.6	Breast	Pos	Pos	Neg	None	0	No	No
49	12.5	SCLC	-	-	-	WBRT	1	No	No
54	3.6	Breast	Pos	Pos	Pos	SRS	0	Yes	Yes
65	3.4	Breast	Pos	Pos	Neg	Spinal cord	0	No	No
73	5.2	Breast	Unk	Unk	Unk	WBRT	1	No	Yes

Extended Data Fig. 2 | Characteristics of patients alive at three months. Clinical characteristics of the 12 patients with leptomeningeal carcinomatosis receiving pembrolizumab who were alive at three months.

All adverse events new or worsening during study occurring in 4 or more patients

All Attributions

Toxicity Description CTCAE v4.0	*01-Mild*	*02-Moderate*	*03-Severe*	*04-Life Threatening*	*05-Fatal*
	N	*N*	*N*	*N*	*N*
Vomiting	7	2	1	-	-
Headache	5	-	3	-	-
Nausea	4	3	2	-	-
Hyperglycemia	8	-	-	-	-
Constipation	7	1	-	-	-
Anorexia	5	1	-	-	-
Fatigue	4	2	-	-	-
Confusion	4	2	-	-	-
Hypokalemia	3	-	2	-	-
Hyponatremia	4	-	1	-	-
Anemia	3	2	-	-	-
Non-cardiac chest pain	3	1	-	-	-
Alanine aminotransferase increased	1	3	-	-	-
Aspartate aminotransferase increased	2	-	2	-	-
Lymphocyte count decreased	-	2	1	1	-
Hypoalbuminemia	4	-	-	-	-
Hypocalcemia	3	1	-	-	-
Muscle weakness lower limb	-	2	2	-	-
Somnolence	3	-	1	-	-

Extended Data Fig. 3 | All adverse events new or worsening during study occurring in 4 or more patients. List of all new or worsening adverse events occurring in 4 patients or more with leptomeningeal carcinomatosis receiving pembrolizumab on study.

Grade 4 and 5 adverse events with attributions		
Case number	***Description***	***Attribution to treatment***
14	Lymphocyte count decreased	Unlikely
	Thrombocytopenia	Unlikely
42	Abdominal pain	Unlikely
55	Respiratory failure	Possible
65	Pneumonia	Unlikely
42	Death	Unlikely
55	Death	Unlikely
65	Death due to respiratory failure	Unlikely
75	Death due to disease progression	Unlikely

Extended Data Fig. 4 | Grade 4 and 5 adverse events with attributions. List of Grade 4 and 5 adverse events in patients with leptomeningeal carcinomatosis receiving pembrolizumab on study.