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Reporting Summary

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Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☐	☒ An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☐	☒ A description of all covariates tested
☐	☒ A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☐	☒ A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☐	☒ For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐ For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐ For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐ Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☐	☒ Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	Clinical data is collected with InForm Software (Version 6.2).
Data analysis	With a historical median overall survival of approximately 5-6 weeks in this patient population, (as determined from previous reports in the literature 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%. Ten patients were to be enrolled in the first stage. If 0 or 1 patients were alive at 3 months, the trial would stop early, due to futility. If 2 or more patients were alive at 3 months, an additional 8 patients would be enrolled. If at least 6 patients among the total of 18 patients were alive at three months, then the treatment would be considered promising in the cohort. This design had a type-I error of 9% (target 10%) and 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 three 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 confidence intervals. Toxicities that were new or worsening relative to baseline are summarized according to the worst grade occurring for each patient. The distribution of overall survival is presented using the method of Kaplan-Meier with 90% confidence intervals estimated using log(-log) methods. Statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

This clinical trial was registered before the start of patient enrollment in www.clinicaltrials.gov (Clinicaltrials.gov identifier NCT02886585)

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	With a historical median overall survival of approximately 5-6 weeks in this patient population, a Simon two-stage design was used to compare a null hypothesis that OS3 would be 18% against an alternative of 43%. Ten patients were to be enrolled in the first stage. If 0 or 1 patients were alive at 3 months, the trial would stop early, due to futility. If 2 or more patients were alive at 3 months, an additional 8 patients would be enrolled. If at least 6 patients among the total of 18 patients were alive at three months, then the treatment would be considered promising in the cohort. This design had a type-I error of 9% (target 10%) and 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 three months; therefore, enrollment continued without pause into the second stage.
Data exclusions	Patients were considered evaluable for primary endpoint if they received at least one cycle of therapy. This was pre-specified in the protocol prior to patient enrollment. A total of 22 patients were consented and accrued to the study, two of whom did not receive study therapy due to subsequent patient decisions not to pursue therapy. The pre-specified analytic cohort consisted of 20 patients who were enrolled and had received at least one dose of pembrolizumab.
Replication	The pre-specified analytic cohort consisted of 20 patients who were enrolled and had received at least one dose of pembrolizumab.
Randomization	This was a single arm Phase II study as there is no standard of care for patients with leptomeningeal disease
Blinding	Blinding is not relevant to this study. This is a single arm Phase II study.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☐	☒ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Human research participants

Policy information about studies involving human research participants

Population characteristics	All patients in the analytic cohort were female, with a median age at the time of study enrollment of 51.5 years (range: 33 to 64; Table 1). Ninety five percent of patients had an ECOG performance status of 0 or 1. Initial diagnosis of breast cancer occurred in

85% of patients (N=17), six of whom had HER-2 positive disease. If only the subset of breast cancer patients is considered, the rates of ER, PR, and 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, 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 to 202 months). Seventy percent of patients had coexisting extracranial disease, with most common sites of lymph node (11) and bone (10). Patients were heavily pre-treated, with all patients having received prior systemic therapy, with a mean of 5 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, 6 patients had undergone radiation both pre- and post-LMD diagnosis, 11 post-LMD only, and one had pre-LMD radiation only. The median time between last brain-directed radiation therapy and enrollment was 3.2 months (range: 0.23 to 21.9 months).

Recruitment

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. The Dana-Farber Harvard Cancer Center (DF/HCC) Institutional review board approved the protocol. Written informed consent was obtained for all participants.
Patients were recruited through our respective institutions predominantly via referral from the solid tumor disease programs and, to a lesser extent, referral from outside physicians. There certainly is an established referral pattern in our institutions whereby patients with breast and lung cancer are more likely to be referred to Neurooncology teams than patients with other solid tumor malignancies. However, the reason for this is that involvement of the central nervous system and, particularly, leptomeningeal metastases in these patients is more common. Further, the availability of standard of care pembrolizumab and other immune checkpoint inhibition as well as molecular targeted therapies is greater in patients with lung cancer and melanoma, which likely led to further selection of patients with breast cancer.