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Palbociclib demonstrates intracranial activity in progressive brain metastases harboring cyclin-dependent kinase pathway alterations

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Recent studies suggest that the cyclin-dependent kinase (CDK) pathway may be a therapeutic target for brain metastases (BM). Here, we present interim analysis of a basket trial evaluating the intracranial efficacy of the CDK inhibitor palbociclib in patients with progressive BM and CDK alterations. Our study met its primary endpoint and provides evidence for performing molecular testing of archival BM tissue, if available, to inform the choice of CNS-penetrant targeted therapy.

A feared complication of solid tumor malignancies is the development of BM, as this results in substantial morbidity and shortened survival. One major roadblock to the development of durable treatments is the paucity of clinical trials designed specifically to evaluate the intracranial efficacy of systemic therapies, due largely to the exclusion of patients with BM because of poor prognosis[1]. Another barrier is genomic heterogeneity between the primary tumor and BM[2,3]. This genomic divergence has important therapeutic implications, as the selection of targeted therapies for BM has traditionally relied on analysis of the primary tumor, given the ease of access to tissue outside the brain.

A logical next step towards developing effective systemic therapies for BM is to leverage these genomic differences between primary, extracranial and intracranial metastases to identify molecular drivers of central nervous system (CNS) tropism. Recent genomic analyses of patient-matched primary tumors and BM implicate the cyclin-dependent kinase (CDK) pathway as a potential contributor to CNS dissemination for tumors of diverse histologies[2,3]. Furthermore, enzymes within the CDK pathway have been implicated as oncogenic drivers and therapeutic targets for several cancers[4,5]. This body of work suggests that CDK alterations may represent a promising therapeutic target for BM. Therefore, we hypothesized that CDK inhibition would result in intracranial efficacy for patients whose tumors harbor such alterations. Given our genomic data, coupled with extensive studies that suggest manageable adverse events, antitumor efficacy[4–7] and possible blood–brain barrier penetration[8] of palbociclib, we proposed a unique, genomically guided, histology-agnostic clinical trial designed specifically for patients with BM to evaluate the intracranial efficacy of palbociclib.

Between February 2017 and September 2019, 15 patients were enrolled (Table 1). Tumor histologies included breast ($n=5$), melanoma ($n=5$), esophageal ($n=3$) and lung ($n=2$). Thirteen patients were enrolled after molecular analysis of intracranial tissue revealed a CDK pathway alteration. An additional two were enrolled using extracranial tissue. The median time between initial cancer diagnosis and study enrollment was 28 months (range = 4–145 months). Eleven patients had coexisting measurable extracranial disease. All patients had received systemic therapies before enrollment, with a median of two previous systemic therapies (standard deviation = 3.7; range = 1–15). Fourteen patients received previous intracranial radiation. Thirteen patients underwent previous brain surgery.

Eight patients had intracranial benefit at 8 weeks after the initiation of palbociclib (Table 2). Intracranial efficacy was observed for all histologies (Supplementary Table 1). All patients with intracranial benefit had stable disease as their best intracranial response. The response assessment in neuro-oncology (RANO) intracranial benefit rate was 53.3% (90% exact confidence interval (CI) = 30–76%). Per prespecified criteria, the overall trial endpoint would be met if six or more patients had intracranial benefit at 8 weeks after enrollment; therefore, our study met the primary endpoint. The median overall survival was 6.4 months (90% CI = 2.8–6.8 months; Fig. 1) from the time of enrollment. The median time to the occurrence of intracranial disease progression (TTP_{CNS}) was 9.0 weeks (90% CI = 6.4–14.0 weeks; Extended Data Fig. 1). The median TTP_{CNS} for the eight patients with intracranial benefit was 6.4 months (90% CI = 3.2–7.9 months). Furthermore, five patients had improvement and an additional four had stability of neurologic symptom burden while taking part in the trial (Supplementary Table 2). Three patients are still alive at time of publication. The median follow-up for these patients has been 29.2 months (range = 26–32 months). All of the patients are off palbociclib. The reasons for discontinuation include: intracranial disease progression (ten); extracranial disease progression (three); unacceptable toxicity (one); and withdrawal of consent (one).

Of the eight patients with intracranial benefit, one had extracranial partial response and three had extracranial stable disease. The extracranial disease burden for two patients was unevaluable

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Table 1 | Patient demographics at enrollment and baseline disease characteristics

	n	%
Gender		
Female	7	46.7
Male	8	53.3
Median age in years (range)	56 (33–80)	
Initial primary tumor diagnosis		
Breast	5	33.3
HR^+HER2^+	1	6.7
HR^-HER2^+	1	6.7
HR^+HER2^-	3	20.0
Triple negative	0	0
Melanoma	5	33.3
Non-small cell lung cancer	2	13.3
Esophageal	3	20.0
ECOG performance status		
0	7	46.7
1	8	53.3
ER status		
Negative	2	13.3
Not applicable	9	60.0
Positive (≥10% expression)	4	26.7
PR status		
Negative	1	6.7
Not applicable	9	60.0
Positive (≥10% expression)	5	33.3
HER2 status		
Negative	4	26.7
Not applicable	9	60.0
Positive	2	13.3
***BRAF* mutation**		
Negative	3	20.0
Not applicable	10	66.7
Positive	2	13.3
***EGFR* mutation**		
Negative	1	6.7
Not applicable	14	93.3
***ALK* mutation'[**		
Negative	1	6.7
Not applicable	14	93.3
CDK pathway alterations		
CDKN2A homozygous loss	12	80.0
Cyclin D1 gain	2	13.3
Cyclin E1 gain	1	6.7
Tissue obtained intracranially	13	86.7
Tissue obtained extracranially	2	13.3
Extracranial metastatic disease	11	73.3
Lymph node	5	45.5
Liver	5	45.5
Lung	3	27.3
Bone	3	27.3
Skin	2	18.2
Chest wall	2	18.2
More than one BM?		
No	2	13.3
Unknown	1	6.7
Yes	12	80.0
Time since initial diagnosis of primary tumor in months (range)	28 (4–145)	
Previous therapy		
Radiation	14	93.3
Intracranial radiation	13	92.9
Whole-brain radiation	2	14.3
Previous brain surgery	12	80.0
Previous systemic therapy	15	100.0
Chemotherapy	11	73.3
Targeted therapy	10	66.7
Immunotherapy	6	40.0

ALK, anaplastic lymphoma kinase; CDKN2A, CDK inhibitor 2A; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; HR, hormone receptor; PR, progesterone receptor.

Table 2 | Summary of response data (RANO and RECIST)

Patient ID	Tumor histology	RANO response (intracranial disease)	RECIST response (extracranial disease)
1[a]	**Breast**	**Stable disease**	**Stable disease**
2	Breast	Progressive disease	Stable disease
3[a]	**Breast**	**Stable disease**	**Unevaluable**
4	Melanoma	Progressive disease	Progressive disease
5[a]	**Melanoma**	**Stable disease**	**Stable disease**
6	Esophageal	Progressive disease	Unevaluable
7[a]	**Lung**	**Stable disease**	**Progressive disease**
8[a]	**Lung**	**Stable disease**	**Progressive disease**
9	Breast	Progressive disease	Missing
10	Melanoma	Progressive disease	Stable disease
11[a]	**Esophageal**	**Stable disease**	**Partial response**
12[a]	**Esophageal**	**Stable disease**	**Progressive disease**
13[a]	**Breast**	**Stable disease**	**Stable disease**
14[b]	**Melanoma**	**Progressive disease**	**Missing**
15[b]	**Melanoma**	**Progressive disease**	**Missing**

[a]These patients had intracranial benefit (that is, complete response, partial response or stable disease, as defined by RANO). [b]These patients were enrolled using extracranial tissue (no intracranial tissue was available at the time of enrollment).

due to a lack of measurable extracranial disease. Three patients did not have systemic restaging scans due to rapidly progressive symptoms that resulted in a transition to hospice. The extracranial rate of response was 7% (90% exact CI = 0.3–28%) and the benefit rate was 40% (90% exact CI = 19–64%). The median time to occurrence of extracranial disease progression ($TTP_{extracranial}$) was 18.7 months (90% CI = 1.9–∞ months; Extended Data Fig. 2).

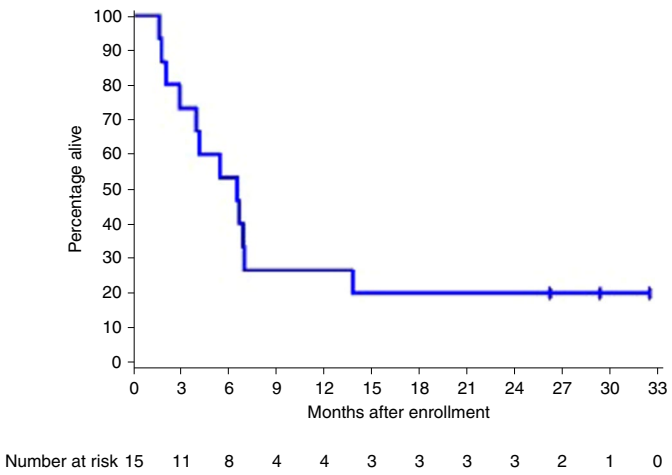

Fig. 1 | Kaplan–Meier curve for overall survival. Kaplan–Meier estimate of overall survival for all of the patients enrolled in the trial ($n=15$). The median overall survival was 6.4 months (90% CI = 2.8–6.8 months). Three patients are still alive at the time of publication and are denoted by the three vertical lines at 26, 29, and 32 months after enrollment.

The median number of cycles completed was two (range = 1–8). Eight patients had cycles delayed, held or reduced. The most common toxicity was hematologic ($n=5$). Of the four patients who required dose reduction, the toxicity profile for three patients resolved with dose reduction and only one patient was taken off the trial (due to febrile neutropenia).

Thirteen patients had one or more adverse events that were at least possibly treatment related (Supplementary Table 3). The most frequently occurring adverse events were anorexia ($n=6$) and fatigue ($n=6$). Seven patients had one or more grade 3 or higher adverse events that were at least possibly related to treatment. The most common grade 3 or 4 adverse event was leukopenia ($n=5$).

Given the increasing incidence of BM, the relative paucity of effective systemic therapies for BM remains a major unmet need in modern oncology. The majority of current clinical trials, especially basket trials, exclude patients with BM. Consequently, many practices for the management of BM are derived from post-hoc or retrospective analyses, which can be prone to non-significant findings or erroneous conclusions due to the testing of multiple hypotheses. Herein, as a direct translation of our genomic characterization studies of BM, we present a successful proof-of-concept study: a genomically guided, histology-agnostic clinical trial designed specifically for patients with BM with the primary objective of gauging the intracranial efficacy of a systemic agent. Our study met its primary endpoint, demonstrating a 53% intracranial benefit rate at 8 weeks with palbociclib in a heavily pretreated population of patients with progressive BM and CDK alterations.

We chose intracranial benefit (which includes stable disease in addition to complete response and partial response) to screen for treatment efficacy, as preclinical studies have demonstrated that single-agent CDK4/6 inhibition prohibits cell cycle progression from the G1 phase to the S phase and therefore results in a potent cytostatic effect for solid tumors of multiple histologies[9,10]. Furthermore, recent trials evaluating palbociclib for other systemic cancers have selected progression-free survival and clinical benefit rate to measure treatment efficacy[7,11,12]. Next, given historical data citing a median overall survival for patients with BM of certain histologies as low as 2.3–5.4 months[1,13–15], we selected 8 weeks to screen for intracranial efficacy, as we anticipated the majority of our cohort would encompass diverse histologies and be heavily pretreated. Furthermore, brain magnetic resonance imaging is generally performed every 8 weeks in clinical practice to monitor BM.

Notably, this study's prespecified primary endpoint was met on the first stage of enrollment. Intracranial efficacy was observed for all histologies. The observed responses were reasonably durable, as the median TTP_{CNS} for the eight patients who experienced intracranial benefit was 6.4 months. Additionally, the median overall survival of 6.4 months compares favorably to the historical median overall survival (3–5 months) for patients with BM[1,13,14]. There were three long-term survivors (overall survival = >2 years) in our cohort, encompassing breast ($n=2$) and melanoma ($n=1$) histologies. The toxicities of palbociclib were clinically noteworthy, as 53% of patients (eight out of 15) required some modification to treatment administration. However, all but one patient's toxicity profile resolved with modified dosing or timing of palbociclib administration, indicating that the majority of adverse events can be managed with dose adjustment and supportive care. Taken together, our study presents encouraging evidence of intracranial antitumor activity through targeting potential oncogenic drivers within BM.

More importantly, our study provides further support for a change in approach for BM treatments, which have historically been centered around surgical resection and radiotherapy. Recently, an increasing number of systemic therapies, such as immune checkpoint inhibitors (ICIs) and targeted therapies for melanoma[16,17] and non-small cell lung cancer[18,19], have demonstrated promising intracranial efficacy, with some studies reporting a response rate of >50%[16,17,19]. Unfortunately, many of these patients still ultimately progress within the CNS[17,20]. New strategies are desperately needed. Therefore, we urge consideration of molecular analysis of BM tissue, if available, to inform the selection of CNS-penetrant targeted therapy. For example, if a patient has a relatively small (<2 cm) and minimally symptomatic BM, a trial of targeted therapy may spare patients the morbidity of a craniotomy or radiation-induced neurotoxicity. Based on these results and our preclinical work[2,3], we have initiated a multi-institutional prospective phase II study (NCT03994796) evaluating the intracranial efficacy of CNS-penetrant therapies (for example, those targeting *CDK*, *PI3K* or *NTRK/ROS1* mutation) in patients with BM harboring these respective genomic alterations.

Our study had several limitations. First, our study had a small sample size and no comparator arm through which to compare other treatment options (radiation or resection). There was also limited overall survival, which may in part be due to the relatively low response and clinical benefit rate extracranially. Furthermore, while our intracranial benefit rate was high at the interim analysis, stable disease was the best observed response. While this was not unexpected given historical data with single-agent CDK inhibition[7,8], analysis of the full cohort of 30 patients and prospective validation is needed before definitive conclusions are drawn regarding the efficacy of palbociclib for BM. Nonetheless, given the dismal prognosis and limited treatments for BM, we feel our interim analysis should be reported, as patients with heavily pretreated BM may benefit from targeted therapies if BM tissue is available and possesses potential driver mutations. In our study, five patients had improvement and an additional four patients had stability of the neurologic symptom burden during treatment (Supplementary Table 2). Another limitation was the inclusion of two patients with extracranial tissue possessing CDK alterations. For these patients (patients #14 and #15 in Table 1), there was no intracranial benefit of palbociclib, underscoring the necessity of molecular analysis of intracranial tissue to inform BM-specific therapeutic regimens. To this end, we are designing trials that evaluate the CNS efficacy of targeted therapy based on molecular analysis of intracranial tissue. An exciting possibility is to evaluate combination regimens, such as CDK inhibition with ICIs, given recent work demonstrating that CDK inhibition has a synergistic effect on tumor immunogenicity when combined with an ICI. Finally, we note the relatively slow accrual rate of 15 patients in 30 months, despite the trial being open at two major academic centers. We attribute this to our pro-

tocol's strong preference for molecular analysis of BM tissue over that of primary tissue, thus limiting trial enrollment to patients able to undergo neurosurgical resection. Therefore, to fully translate the potential vulnerabilities of a BM into clinical practice, a critical future step is to develop noninvasive techniques for molecular analysis of BM.

In conclusion, we present a novel clinical trial design in which we evaluated the intracranial efficacy of CDK inhibition in patients with BM and CDK alterations. While our trial met its primary endpoint, our conclusions are tempered by the small cohort. We recommend consideration of molecular analysis of archival BM tissue, if available, to inform the choice of CNS-penetrant targeted therapy. Most importantly, we urge future planning of basket trials tailored specifically for patients with BM to gauge the intracranial efficacy of systemic agents targeting potential oncogenic drivers. These studies will facilitate the development of new therapeutics for BM—an area of extraordinary need within modern oncology.

Methods

Study oversight. This study (ClinicalTrials.gov identifier: NCT02896335) was designed by P.K.B. and conducted in accordance with the provision of the Declaration of Helsinki and Good Clinical Practice guidelines (Extended Data Fig. 1). The Dana-Farber/Harvard Cancer Center (DF/HCC) Institutional Review Board (IRB) approved the protocol. Funding was provided by Pfizer, the Damon Runyon Cancer Research Foundation and Massachusetts General Hospital.

Patients. Eligible patients had disease that had been confirmed histologically from any metastatic solid tumor and measurable disease in the CNS, defined as at least one metastasis that could be measured in at least one dimension as ≥10 mm. Patients had to have had progressive CNS metastases immediately before enrollment. Previous BM-directed therapies, such as radiation and systemic therapies with CNS penetration, were allowed. For patients with previous intracranial radiation, there had to be unequivocal evidence of progression of at least one lesion treated by radiation (for example, tissue confirmation). Participants who had received chemotherapy, immunotherapy or radiotherapy within 2 weeks before trial enrollment were excluded. Concurrent radiation or systemic therapy, other than aromatase/hormone inhibition or ovarian suppression, were not allowed. Other key inclusion criteria were as follows: the presence of CDK pathway alteration on tumor tissue (intracranial tissue strongly preferred if available); age ≥ 18 years, Eastern Cooperative Oncology Group performance status ≤ 2; and a stable dose of corticosteroids for at least 7 d before the start of the trial. Key exclusion criteria included: leptomeningeal involvement of cancer; and previous treatment with a CDK4/6 inhibitor. All patients provided signed informed consent forms.

Study design, treatment and endpoints. Palbociclib was administered orally at 125 mg daily until disease progression, death, unacceptable toxicity or study consent withdrawal. Treatment was administered daily for 21 d, followed by 7 d off, to complete a 28-d cycle. Dose reduction of palbociclib by one dose level (25 mg) and, if needed, by two dose levels (50 mg) was recommended depending on the type and severity of toxicity. Once a dose had been reduced for a given patient, all subsequent cycles were administered at that dose level, unless further dose reduction was required. Dose re-escalation was not allowed. Patients requiring more than two dose reductions were discontinued from the study.

Brain magnetic resonance imaging plus computed tomography of the chest, abdomen and pelvis was obtained every 8 weeks for restaging. Intracranial and extracranial efficacies were assessed centrally via blinded review by the Massachusetts General Hospital Tissue Imaging Metrics Core using RANO[21] and response evaluation criteria in solid tumors (RECIST) 1.1 (ref. [22]) criteria, respectively. The primary endpoint was intracranial benefit (complete response, partial response or stable disease) at 8 weeks. Under these criteria, complete response was defined as the disappearance of all CNS target lesions. Partial response was defined as a ≥30% decrease in the sum of the longest diameters in CNS target lesions relative to the baseline sum of the longest diameters, without new CNS lesions. Stable disease was defined as a <30% decrease and a <20% increase in the sum of the longest diameters of target lesions relative to the baseline sum of the longest diameters, without new CNS lesions. Secondary endpoints included: extracranial benefit rate (defined as complete response, partial response or stable disease, per RECIST); TTP_{CNS}; $TTP_{extracranial}$; overall survival; and toxicity using Common Terminology Criteria for Adverse Events version 5.0. Additionally, each patient's estimated prognosis, from the time of the initial diagnosis of BM, was calculated using the diagnosis-specific Graded Prognostic Assessment[15].

Statistics and reproducibility. This clinical trial was designed as an open-label, single-arm phase II clinical trial. We employed a two-stage Simon design comparing the proportion of patients with intracranial benefit under a null hypothesis response rate of 10% against an alternative of 30%. Fifteen patients were enrolled in the first stage, at which point a prespecified interim analysis was carried out. If there were fewer than two responders, the study would stop for insufficient evidence of efficacy. If there were at least two patients with intracranial benefit among the first 15 patients, we would enroll an additional 15 patients for a total of 30 patients for final analysis. If there were six or more total responders, the overall primary endpoint would be met and palbociclib would be considered worthy of further study. This design has a type I error of no more than 7% (target 10%) and a power of 91% (target 90%) for the entire cohort of 30 patients. If the true response is 10%, the probability is 0.55 of stopping at the end of the first stage. No data were excluded from the analyses. There was no randomization of patients, as this was a single-arm phase II study.

The intracranial and extracranial benefit rates are summarized along with 90% exact binomial CIs. Toxicities that were new or worsening relative to the baseline are summarized according to the worst grade occurring for each patient. The distribution of overall survival is presented using the Kaplan–Meier method, with 90% CI estimates using log(-log) methods. Clinical data were collected using InForm Software (version 6.2). Data analysis was performed using Stata (version 16).

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

Data availability

The authors confirm that the data supporting the findings of this study are available within the article and its Supplementary Information. Any requests for additional data (e.g., clinical outcomes, tissue samples) should be sent to P.K.B. and will be reviewed by the DF/HCC IRB. Patient-related data not included in the paper were generated as part of a clinical trial and are subject to patient confidentiality. Any data that can be shared will need approval from the DF/HCC IRB and a Material Transfer Agreement in place. All data shared will be deidentified. Source data are provided with this paper. All other data supporting the findings of this study are available from the corresponding author upon request. Please note that any materials (for example, tissue samples or imaging data) that can be shared will need approval from the DF/HCC IRB and a Material Transfer Agreement in place. All materials shared will be deidentified.

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Author contributions

P.K.B., R.J.S., S.L.C. and D.P.C. conceived of the study idea. P.K.B. wrote the protocol with input from R.J.S., D.P.C., S.L.C., S.S., T.T.B., A.G.-H., E.R.G. and K.O. A.E.K., N.W., E.Q.L., J.L., J.V.C., U.N.C., D.F., M.D.W., H.A.S., J.F.G., R.S.H., M.M., E.R.G., K.O., D.L., D.P.R., D.P.C. and R.J.S. supported the clinical trial, including recruitment and/or management of patients on the trial. A.J.I. assisted with the genetic profiling analysis. A.G.-H. performed the statistical analysis. E.R.G. was the imaging chair of the study. P.K.B., A.E.K., 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, Voyager Therapeutics, AngioChem, Genentech/Roche, ElevateBio, SK Life Science, Dantari, Pfizer and Lilly; has received research funding (to Massachusetts General Hospital) from Merck, Mirati, Lilly, BMS and Pfizer; and has received honoraria from Merck and Genentech/Roche. N.W. has received compensation from Seattle Genetics and Wolters Kluwer; and has research funding (to institution, not self) from Merck. E.Q.L. has received royalties from Wolters Kluwer (UpToDate) and has consulted for Lilly. J.V.C. has received consulting fees from Sanofi/Genzyme and BMS. H.A.S. serves on the Board of Directors for the Radiosurgery Society and has received compensation from Wolters Kluwer (UpToDate). D.F. has stock ownership (<$10,000) in Eli Lilly. J.F.G. has served as a compensated consultant or received honoraria from Bristol-Myers Squibb, Genentech, Ariad/Takeda, Loxo/Lilly, Blueprint, Oncorus, Regeneron, Gilead, AstraZeneca, Pfizer, Novartis, Merck, and GlydeBio; research support from Novartis, Genentech/Roche, and Ariad/Takeda; institutional research support from Bristol-Myers Squibb, Tesaro, Moderna, Blueprint, Jounce, Array Biopharma, Merck, Adaptimmune, Novartis, and Alexo; and has an immediate family member who is an employee with equity at Ironwood Pharmaceuticals. R.S.H. has received consulting honoraria from Novartis, Daichii Sankyo, EMD Serono, Boehringer Ingelheim, Tarveda, Apollomics; and has research funding (to institution, not to self) from Agios, Abbvie, Daichii Sankyo, Novartis, Lilly, Mirati, Corvus, Genentech Roche, Exelixis, Turning Point. D.P.R. holds equity in MPM Capital and Acworth Pharmaceuticals; has served as a paid consultant and/or on an advisory board for MPM Capital, Oncorus, Gritstone Oncology, Maverick Therapeutics, and Boehringer Ingelheim; and has received compensation from Johns Hopkins University Press, Wolters Kluwer (UpToDate), and McGraw Hill. A.J.I. holds equity in Invitae, and has consulted for Paige.AI, Kinnate, Repare, and Oncoclinicas Brasil. S.S. has consulted for RareCyte, Inc. D.P.C. has consulted for Lilly, GSK, and Boston Pharmaceuticals and has received travel/speaking fees from Merck. R.J.S. has received research funding from Amgen and Merck and served as a paid consultant and/or on an advisory board for Array BioPharma, Amgen, Asana BioSciences, AstraZeneca, BMS, Compugen, Eisai, Genentech, Merck, Novartis, OncoSec, Pfizer and Replimune.

Additional information

Extended data is available for this paper at https://doi.org/10.1038/s43018-021-00198-5.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s43018-021-00198-5.

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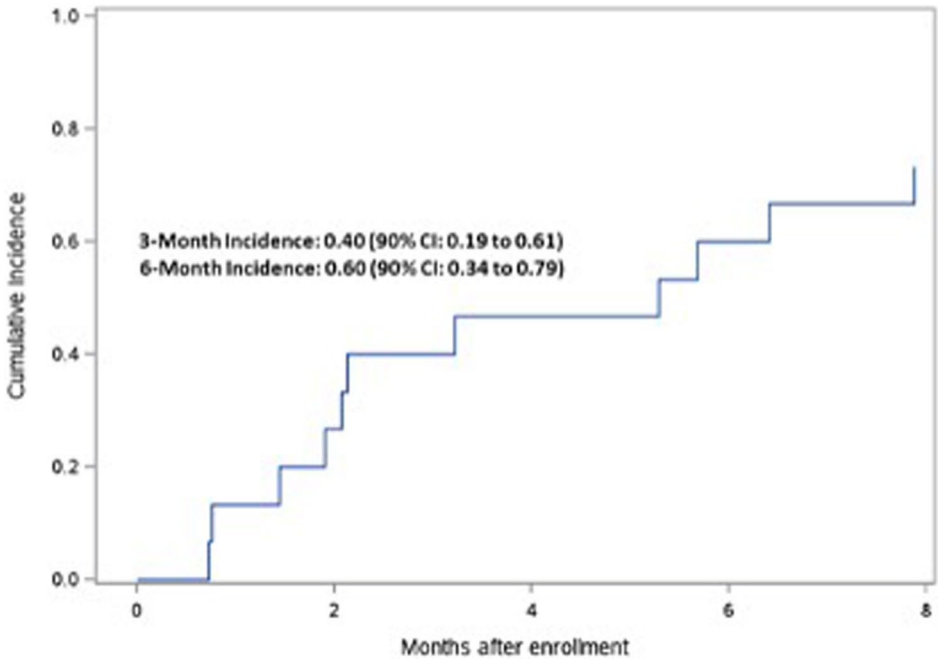
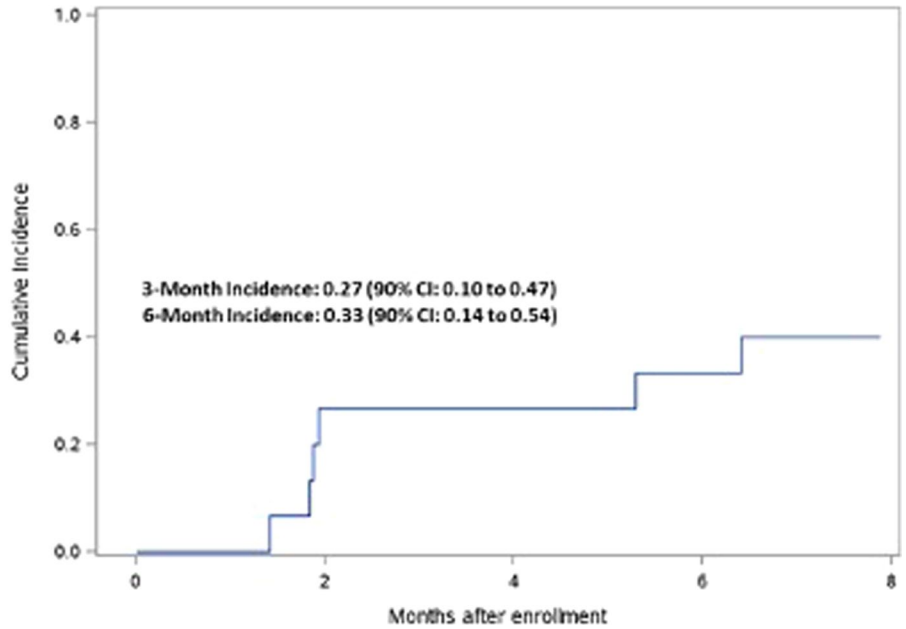
Peer review information *Nature Cancer* thanks Frédéric Dhermain, Priya U. Kumthekar and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.



Extended Data Fig. 1 | Cummulative Incidence of Intracranial Progression-Free Survival, with Extracranial Progression as a Competing Risk. Competing risk analysis was performed for all 15 patients enrolled on trial. At 6 months, the proportion of patients who were intracranial progression free was 0.60 (90% CI: 0.34-0.79).



Extended Data Fig. 2 | Cummulative Incidence of Extracranial Progression-free Survival, with Intracranial Progression as a Competing Risk. Competing risk analysis was performed for the 10 patients with evaluable systemic imaging. At 6 months, the proportion of patients extracranial progression free was 0.33 (90% CI: 0.14-0.54).

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☒	☐	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
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Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	Clinical data was collected with InForm Software (version 6.2)
Data analysis	Commercially available statistical software packages (Stata version 16) was used for data analysis.

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 and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

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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
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Data Availability Statement: The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials. Any requests for additional data should be sent to Dr. Priscilla Brastianos (pbrastianos@mgh.harvard.edu) and will be reviewed by the DF/HCC Institutional Review Board (IRB). Patient-related data not included in the paper were generated as part of a clinical trial and are subject to patient confidentiality. Any data that can be shared will need approval from the DF/HCC IRB and a Material Transfer Agreement in place. All data shared will be deidentified.
Materials Availability Statement: Any materials (e.g. tissue samples or imaging data) that can be shared will need approval from the DF/HCC IRB and a Material Transfer Agreement in place. All materials shared will be deidentified.

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For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

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

Sample size	We employed a Simon two-stage design comparing the proportion of patients with intracranial benefit under a null hypothesis response rate of 10% against an alternative of 30%. Fifteen patients were enrolled in the first stage. A pre-specified interim analysis was carried out at 15 patients. If there were fewer than two responders, the study would stop for insufficient evidence of efficacy. If there were at least two patients with intracranial benefit in the first 15 patients, we would enroll an additional 15 patients for a total of 30 patients for final analysis. If there were 6 or more total responders, the overall primary endpoint would be met and palbociclib will be considered worthy of further study. This design has a type-I error of no more than 7% (target 10%) and power of 91% (target 90%) for the entire cohort of 30 patients. If the true response is 10%, then the probability is 0.55 of stopping at the end of the first stage.
Data exclusions	No data was excluded.
Replication	Replication of findings could not be performed, as we are reporting pre-specific interim analysis of a phase II clinical trial.
Randomization	There was no randomization of patients in our study, as this was a single arm phase II study.
Blinding	Blinding was not possible for our study, as this was a single arm phase II study.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☐	☒ Human research participants
☐	☒ Clinical data
☒	☐ Dual use research of concern

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	Eligible patients had histologically confirmed disease from any metastatic solid tumor and measurable disease in the CNS, defined as at least one metastasis that can be measured in at least one dimension as > 10 mm. Patients must have had progressive CNS metastases immediately prior to enrollment. Prior BM-directed therapies, such as radiation and systemic therapies with CNS penetration, were allowed. For patients with prior intracranial radiation, there must be unequivocal evidence of progression of at least one lesion treated by radiation (e.g. tissue confirmation). Participants who had chemotherapy, immunotherapy, or radiotherapy within 2 weeks prior to trial enrollment were excluded. Concurrent radiation or systemic therapy, other than aromatase/hormone inhibition or ovarian suppression, were not allowed. Other key inclusion criteria included the following: presence of CDK pathway alteration on tumor tissue (intracranial tissue strongly preferred if available), age > 18, ECOG performance status < 2, and stable dose of corticosteroids for at least 7 days prior to start of trial. Key exclusion criteria included leptomeningeal involvement of cancer and prior treatment with a CDK4/6 inhibitor. There were 7 female and 8 male subjects in our study. The median age was 56 (range: 33-80). 5 patients had breast cancer, 5 patients had melanoma, 2 patients had non-small cell lung cancer, and 3 patients had esophageal cancer.
Recruitment	Patients were recruited through the Massachusetts General Hospital Central Nervous System Metastasis Clinic and the Dana-

Recruitment	Farber Cancer Institute Division of Neuro-Oncology. It is possible that geographic and socioeconomic factors that determine access to our institutions at the DF/HCC may have been a source of selection bias.
Ethics oversight	The Dana-Farber Harvard Cancer Center (DF/HCC) Institutional Review Board approved the protocol.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about clinical studies

All manuscripts should comply with the ICMJE guidelines for publication of clinical research and a completed CONSORT checklist must be included with all submissions.

Clinical trial registration	Clinicaltrials.gov identifier NCT02896335
Study protocol	The full clinical trial protocol was provided with manuscript submission.
Data collection	Study data files were retrieved for this report on February 25, 2020 with 15 patients enrolled. The first patient was enrolled on February 14, 2017 and the last patient for this analysis was enrolled on September 16, 2019. Clinical research coordinators and physicians collected salient clinical information for each patient. All data was collected at the MGH Cancer Center Protocol Office.
Outcomes	The primary endpoint was intracranial benefit (complete response (CR), partial response (PR), or stable disease (SD)) at 8 weeks. . Secondary endpoints include extracranial benefit rate (defined as CR, PR, or SD, per RECIST), time to occurrence of intracranial (TTPCNS) and extracranial disease progression (TTPextracranial), overall survival (OS), and toxicity using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.