original reports

Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis

Jonathan T. Yang, MD, PhD[1]; N. Ari Wijetunga, MD, PhD[1]; Elena Pentsova, MD[2]; Suzanne Wolden, MD[1]; Robert J. Young, MD[3]; Denise Correa, PhD[2]; Zhigang Zhang, PhD[4]; Junting Zheng, MS[4]; Alexa Steckler, BS[1]; Weronika Bucwinska, BS[1]; Ashley Bernstein, CTN[1]; Allison Betof Warner, MD, PhD[5]; Helena Yu, MD[6]; Mark G. Kris, MD[6]; Andrew D. Seidman, MD[7]; Jessica A. Wilcox, MD[2]; Rachna Malani, MD[2]; Andrew Lin, MD[2]; Lisa M. DeAngelis, MD[2]; Nancy Y. Lee, MD[1]; Simon N. Powell, MD, PhD[1]; and Adrienne Boire, MD, PhD[2,8]

abstract

PURPOSE Photon involved-field radiotherapy (IFRT) is the standard-of-care radiotherapy for patients with leptomeningeal metastasis (LM) from solid tumors. We tested whether proton craniospinal irradiation (pCSI) encompassing the entire CNS would result in superior CNS progression-free survival (PFS) compared with IFRT.

PATIENTS AND METHODS We conducted a randomized, phase II trial of pCSI versus IFRT in patients with non–small-cell lung cancer and breast cancers with LM. We enrolled patients with other solid tumors to an exploratory pCSI group. For the randomized groups, patients were assigned (2:1), stratified by histology and systemic disease status, to pCSI or IFRT. The primary end point was CNS PFS. Secondary end points included overall survival (OS) and treatment-related adverse events (TAEs).

RESULTS Between April 16, 2020, and October 11, 2021, 42 and 21 patients were randomly assigned to pCSI and IFRT, respectively. At planned interim analysis, a significant benefit in CNS PFS was observed with pCSI (median 7.5 months; 95% CI, 6.6 months to not reached) compared with IFRT (2.3 months; 95% CI, 1.2 to 5.8 months; $P < .001$). We also observed OS benefit with pCSI (9.9 months; 95% CI, 7.5 months to not reached) versus IFRT (6.0 months; 95% CI, 3.9 months to not reached; $P = .029$). There was no difference in the rate of grade 3 and 4 TAEs ($P = .19$). In the exploratory pCSI group, 35 patients enrolled, the median CNS PFS was 5.8 months (95% CI, 4.4 to 9.1 months) and OS was 6.6 months (95% CI, 5.4 to 11 months).

CONCLUSION Compared with photon IFRT, we found pCSI improved CNS PFS and OS for patients with non–small-cell lung cancer and breast cancer with LM with no increase in serious TAEs.

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INTRODUCTION

Leptomeningeal metastasis (LM), the spread of a malignancy into the CSF-filled leptomeningeal space surrounding the brain and spinal cord, is associated with marked morbidity and mortality. LM is clinically detected in 5%-10% of patients with solid tumors[1] but is frequently underdiagnosed; approximately 30% of all patients with malignancy and neurologic symptoms harbor LM at autopsy.[2-4] The incidence of LM is rising, likely because of improved imaging techniques[5] and systemic disease control.[6-8] LM incidence varies widely depending on histology, with lung cancer and breast cancer being most associated with LM (5%-25%), followed by melanoma (6%-18%) and gastrointestinal malignancies (4%-14%).[3,5,9,10]

Once within the leptomeningeal space, tumor cells disseminate throughout the CNS. As a result, patients with LM may develop multiple debilitating neurologic dysfunctions that can be life-threatening. Treatments for LM are palliative with the goals of stabilizing or improving neurologic symptoms. The prognosis for patients with LM is poor. Untreated LM can lead to death within 4-6 weeks. With treatments, the overall survival (OS) remains poor at between 4-6 months.[5,11] Responses to therapies and outcomes vary widely and are affected by performance status, tumor histology, and disease outside the CNS.[10,12-16]

Radiotherapy (RT) effectively relieves local symptoms because of LM, and, in the form of photon involved-field RT (IFRT), is commonly used to treat symptomatic or bulky disease sites.[17-19] Because LM disseminates throughout the entire CNS compartment, standard-of-care IFRT, such as whole-brain radiotherapy (WBRT) or focal spine RT, cannot halt the progression of LM

ASSOCIATED CONTENT
Appendix
Protocol
Author affiliations and support information (if applicable) appear at the end of this article.
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CONTEXT

Key Objective

Solid tumor leptomeningeal metastasis (LM) is associated with significant morbidity and mortality. Standard-of-care photon involved-field radiotherapy (IFRT) is effective in relieving local symptoms because of LM; however, it does not stop progression of LM along the neuroaxis. We tested whether proton craniospinal irradiation (pCSI) would improve progression-free survival compared with IFRT. This phase II trial is the first randomized evaluation of the optimal radiotherapy approach for LM.

Knowledge Generated

pCSI resulted in significantly improved CNS progression-free survival compared with IFRT in patients with metastatic non–small-cell lung cancer and breast cancer with LM, meeting the primary end point of the study, which led to early discontinuing of the trial at planned interim analysis. pCSI also showed overall survival advantage compared with IFRT with no increase in high-grade adverse events.

Relevance

Our results support the superior efficacy in CNS disease control of pCSI compared with standard-of-care IFRT in patients with non–small-cell lung cancer and breast cancer LM. Additional investigation is warranted to evaluate the observed overall survival benefit of pCSI.

along the entire neuroaxis. Craniospinal irradiation (CSI), conversely, treats the whole leptomeningeal compartment and may therefore achieve superior symptom and disease control. In fact, photon CSI has demonstrated efficacy with LM in retrospective studies, but toxicities limit the widespread applicability of this technique.[20] When delivering photon radiation to the entire neuroaxis, photons exit the body anteriorly, exposing the entire spinal column and anterior organs to radiation. This can lead to unacceptable toxicities in patients who already have significant morbidities. By contrast, when using protons for CSI, most commonly, protons are planned to deposit the bulk of their energy at the last few millimeters of their range, resulting in diminished delivery of radiation beyond the neuroaxis and significantly less toxicity.[21]

We had previously identified in a phase Ib clinical trial that hypofractionated proton CSI (pCSI) at a dose of 3 Gy × 10 fractions is a safe treatment for patients with solid tumor LM with promising long-term CNS control observed.[22] Here, we report the results of a randomized phase II trial of pCSI versus standard-of-care photon IFRT in patients with LM.

PATIENTS AND METHODS

Study Design and Participants

We conducted an open-label, randomized, phase II trial to assess the efficacy of pCSI in patients with pathologically proven solid tumor malignancies with LM established radiographically and/or through CSF cytology. Additional eligibility criteria included Karnofsky performance score ≥ 60; ability in developing a treatment plan respective of normal tissue tolerance; and adequate bone marrow function. Patients with treated and untreated parenchymal brain metastases were eligible. Systemic therapy was held during protocol therapy. Patients resumed or began new systemic therapy per physician's choice after protocol therapy. The Protocol (online only) was approved by the Memorial Sloan Kettering Cancer Center institutional review board, registered with ClinicalTrials.gov identifier (NCT04343573), and completed in accordance with the protocol and Good Clinical Practice guidelines. All patients provided informed consent.

Random Assignment and Masking

Patients with metastatic non–small-cell lung cancer (NSCLC) or breast cancer were randomly assigned in a 2:1 ratio to pCSI versus standard-of-care photon IFRT, stratified by histology (NSCLC *v* breast) and systemic disease status (progressive *v* stable/none). Patients with other solid tumor histologies were enrolled to an exploratory pCSI group without random assignment.

Procedures

Pretreatment evaluations included history and physical examination; complete blood count, electrolytes, and renal and liver function tests; lumbar puncture for CSF assessment, including cytology and circulating tumor cell (CTC) using CellSearch platform[23]; and contrast-enhanced magnetic resonance imaging of the neuroaxis. Protocol RT was delivered at a dose of 3 Gy × 10 daily fractions, with RT planning time ≤ 2 weeks per protocol. Cumulative dose-volume constraint guidelines for organs at risk were followed (Appendix Table A1, online only). Patients who received pCSI were treated with pencil beam scanning proton therapy to the entire CNS compartment.[24] Patients who received photon IFRT, including WBRT and/or focal spine RT, underwent three-dimensional planning to symptomatic sites. All patients received memantine prophylaxis.[25] During protocol therapy, patients underwent weekly clinical assessment and complete blood count. Patients were

followed every 3 months with repeat neuroaxis magnetic resonance imaging and lumbar puncture for up to 1 year or until CNS progression. Treatment-related adverse events (TAEs, Common Terminology Criteria for Adverse Events version 5.0) were assessed weekly during protocol therapy and at each follow-up.

Outcomes

The primary end point was CNS progression-free survival (CNS PFS), defined as the time from random assignment to CNS disease progression or death among patients with NSCLC and breast cancer randomly assigned to pCSI versus IFRT. Patients were censored at the last follow-up (April 11, 2022) or the date of withdrawal from the study per protocol. Patients with new neurologic deficits not related to therapeutic intervention, progressive radiographic change using Leptomeningeal Assessment in Neuro-Oncology scale,[26] and/or new positive CSF cytology after previously negative CSF cytology were considered to have progression. Enrollment of 81 patients with NSCLC and breast cancer LM would provide a one-sided α of .025 and power of 0.8 on the basis of stratified log-rank test for an estimated CNS PFS of 3 months for IFRT and 6 months for pCSI. An interim analysis was planned after half of the expected events were observed (25 events). Lan-DeMets spending function was used. At the interim analysis, if $P < .0015$ favoring pCSI, the trial would stop for efficacy. If $P > .288$, the trial would stop for futility. At the final analysis, we would declare the pCSI superior if $P < .024$ favoring pCSI.

Secondary end points included OS, defined as the time from random assignment to death or last on study follow-up, and TAEs. Protocol-defined exploratory end points included outcomes for patients with other solid tumor histologies enrolled on the exploratory pCSI group, and evaluation of the utility of CSF CTC as a potential biomarker.

Statistical Analysis

The Kaplan-Meier method was used to estimate CNS PFS and OS. The cumulative incidence was estimated for time to CNS progression (CNS TTP) with death treated as a competing event. For patients in the randomized groups, stratified log-rank test and stratified Gray's test were used to compare CNS TTP, CNS PFS, and OS. Multivariable Cox proportional hazard regressions were performed to examine associations of CNS PFS and OS with treatment, age, Karnofsky performance score, histology, and systematic disease status. Backward variable selection on the basis of z test was applied. TAEs were reported for all patients. Incidences of high-grade TAEs (grade ≥ 3 nonhematologic toxicities and grade ≥ 4 hematologic toxicities) were compared between the randomized groups using the chi-squared test with Rao and Scott's[27] second-order correction to take into account multiple adverse events per patient.

As an exploratory assessment, CSF CTC count and its correlation with outcomes were analyzed. Baseline CTC count was analyzed as a categorical predictor dichotomized by the median count. We tested whether there was a significant interaction between baseline CTC count and treatment groups, and reported association of CTC count with CNS TTP, CNS PFS, and OS. We then analyzed CTC counts over time (baseline and after protocol therapy) as described previously with joint modeling of longitudinal and survival outcomes with shared random effects and an unspecified baseline risk function,[23] allowing modeling of a linear mixed-effect model that is then used as a predictor in a Cox proportional hazard model. The interpretation of the joint model coefficients reveals whether trends in CTC count over time are associated with outcomes.[28] We modeled the relationship between CTC counts over time and CNS TTP (censored at death or no CNS progression), CNS PFS, and OS, comparing the randomized pCSI and IFRT groups, adding fixed-effect terms to the model for treatment arm, histology, and their interaction. The results from models treating CTC count as a continuous covariate were reported per 10-cell increment. The association between treatment group and histology was determined using analysis of variance of nested JM models. All statistical analyses were performed in R version 4.1 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Between April 16, 2020, and October 11, 2021, 63 NSCLC and breast cancer patients with LM were randomly assigned to either pCSI (n = 42) or photon IFRT (n = 21), and 35 patients with other solid tumor histologies with LM were enrolled to an exploratory pCSI group (Fig 1). Baseline demographic and relevant clinical variables were not different between the randomized groups (Table 1).

Randomized pCSI Versus Photon IFRT for Patients With NSCLC and Breast Cancer LM

At the time of analysis, 12/42 patients in the pCSI group experienced CNS progression (five with radiographic and clinical progression, two with clinical progression, two with CSF cytologic progression, two with radiographic progression, and one with radiographic and CSF cytologic progression), and 16/21 patients in the IFRT group experienced CNS progression (seven with radiographic and clinical progression, four with clinical progression, three with radiographic progression, and two with CSF cytologic and clinical progression). Of the 16/42 pCSI patients who died, eight died with systemic disease progression, four with CNS and systemic disease progression, and four with CNS progression. Of the 14/21 IFRT patients who died, nine died with CNS progression, and five died with CNS and systemic disease progression. The median duration of follow-up was 9.3 months (95% CI, 7.8 to 17.6 months; range: 0-18.9 months).

pCSI patients had significantly longer estimated CNS TTP compared with those who received photon IFRT

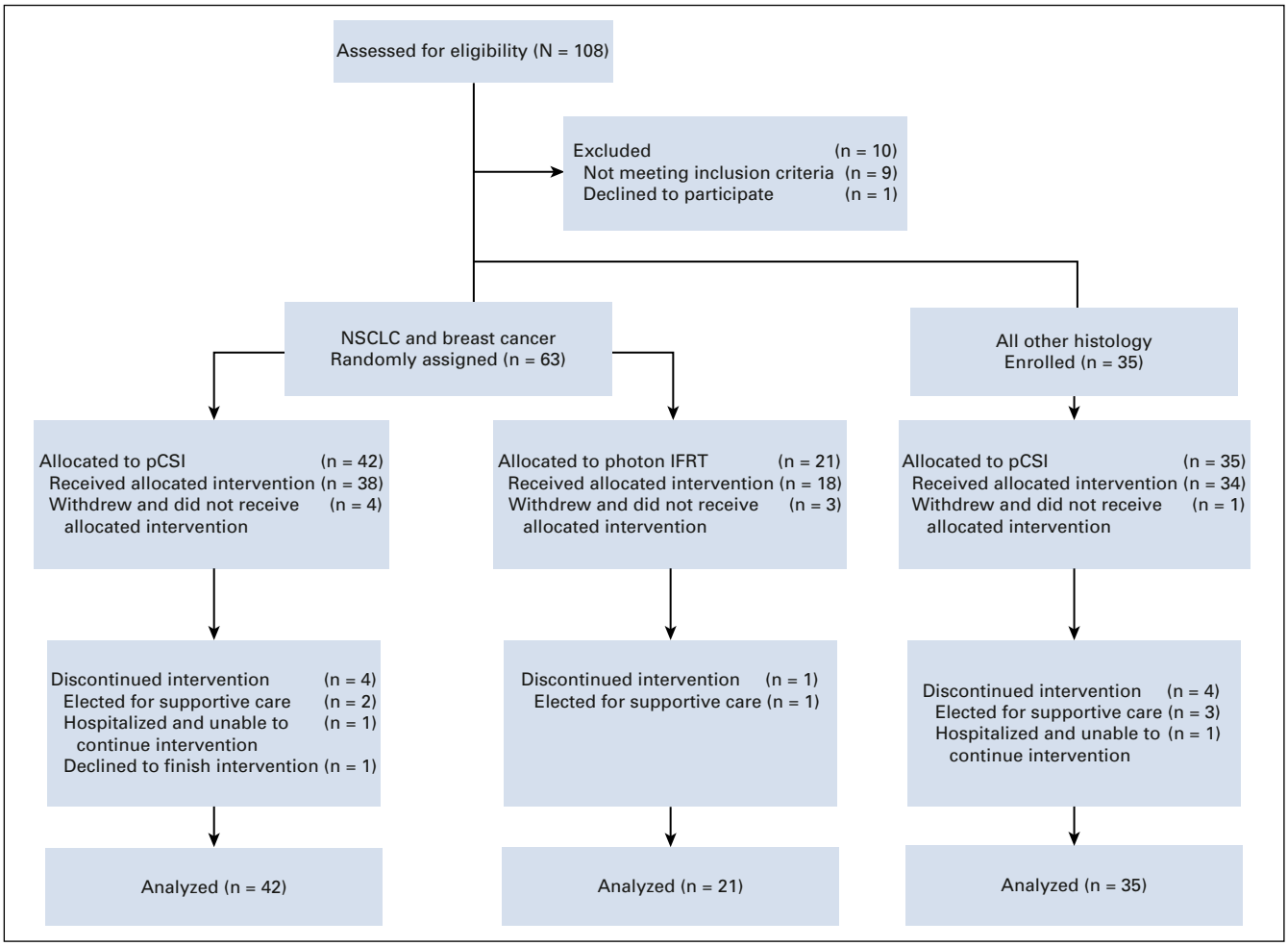

FIG 1. CONSORT diagram. IFRT, involved-field radiotherapy; NSCLC, non–small-cell lung cancer; pCSI, proton craniospinal irradiation.

($P < .001$), with 6.3% (95% CI, 1.1 to 18) and 22% (95% CI, 9.5 to 38) of pCSI patients and 70% (95% CI, 40 to 87) and 92% (95% CI, 37 to 99) of IFRT patients experiencing CNS progression at 3 months and 6 months, respectively (Fig 2A). Significant improvement in CNS PFS was observed with pCSI, with a median CNS PFS of 7.5 months (95% CI, 6.6 months to not reached) compared with 2.3 months (95% CI, 1.2 to 5.8 months; $P < .001$; Fig 2B) with IFRT. As a result, the Memorial Sloan Kettering Cancer Center Data and Safety Monitoring Committee recommended early discontinuation of the trial. In addition, an OS benefit with pCSI was observed with median OS of 9.9 months (95% CI, 7.5 months to not reached) compared with 6.0 months (95% CI, 3.9 months to not reached; $P = .029$; Fig 2C) with IFRT. In a multivariable analysis, pCSI remained significantly associated with improved CNS PFS (hazard ratio [HR], 0.15; 95% CI, 0.07 to 0.33; $P < .001$) and OS (HR, 0.43; 95% CI, 0.21 to 0.90; $P = .025$; Table 2).

TAEs were similar between groups (Appendix Table A2, online only). No patient in either group experienced grade 5 toxicity. In the pCSI group, lymphopenia was the only grade 4 TAE reported (n = 4; 10%). Grade 3 nonhematologic toxicities included fatigue (n = 1; 2%), pain (n = 1; 2%), and vomiting (n = 1; 2%). In the IFRT group, lymphopenia was the only grade 4 TAE reported (n = 4; 19%). Grade 3 nonhematologic toxicities included fatigue (n = 2; 10%), gait disturbance (n = 1; 5%), and headache (n = 1; 5%). There was no difference in the rate of high-grade TAE between the two cohorts ($P = .19$).

Exploratory pCSI for Patients With Other Solid Tumor Histologies

The most common histology in the exploratory pCSI group was ovarian cancer (n = 7; 20%), followed by esophageal cancer (n = 6; 17%) and melanoma (n = 6; 17%). At the time of analysis, 9/35 patients experienced CNS progression (four with radiographic and clinical progression, two with clinical progression, two with radiographic progression, one with CSF cytologic progression), and 23/35 patients died (11 with systemic disease progression, five with CNS progression, four with CNS and systemic disease progression). The median duration of follow-up was 12 months (95% CI, 6.3 months to not reached;

TABLE 1. Clinical Characteristics of All Evaluable Patients (N = 98)

Characteristic	Randomized pCSI Group	Randomized Photon IFRT Group	Exploratory pCSI Group
No. of patients	42	21	35
Median age at registration, years (range)	57 (37-79)	61 (31-75)	61 (27-77)
Sex, No. (%)			
Female	34 (81)	18 (86)	20 (57)
Male	8 (19)	3 (14)	15 (43)
KPS, median (range)	80 (60-90)	80 (60-90)	80 (60-90)
Histology, No. (%)			
NSCLC	24 (57)	12 (57)	
EGFR+	12 (29)	7 (33)	
Targeted therapy before enrollment			
Osimertinib	12 (29)	7 (33)	
ALK/ROS1+	2 (5)		
Targeted therapy before enrollment			
Alectinib	1 (2)		
Lorlatinib	1 (2)		
Breast	18 (43)	9 (43)	
HER2+	6 (14)	4 (19)	
Targeted therapy before enrollment			
Tucatinib	2 (5)	1 (5)	
Trastuzumab emtansine	2 (5)		
Trastuzumab deruxtecan		1 (5)	
Lapatinib	1 (2)	1 (5)	
Trastuzumab	1 (2)	1 (5)	
Ovarian			7 (20)
Esophageal			6 (17)
Melanoma			6 (17)
Colorectal			5 (14)
Head and neck			3 (9)
Pancreatic			2 (6)
SCLC			2 (6)
Anal			1 (3)
Biliary			1 (3)
Prostate			1 (3)
Unknown primary			1 (3)
Systemic disease status at enrollment, No. (%)			
Active	22 (52)	11 (52)	20 (57)
Stable/none	20 (48)	10 (48)	15 (43)
Baseline evaluation, No. (%)			
Positive MRI	38 (91)	21 (100)	33 (94)
Positive cytology	28 (67)	11 (52)	23 (66)
Parenchymal brain metastases at enrollment, No. (%)			
Yes	28 (67)	15 (71)	12 (34)
No	14 (33)	6 (29)	23 (66)

(continued on following page)

TABLE 1. Clinical Characteristics of All Evaluable Patients (N = 98) (continued)

Characteristic	Randomized pCSI Group	Randomized Photon IFRT Group	Exploratory pCSI Group
Median lines of prior systemic therapy received for metastatic disease (range)	2 (0-8)	2 (0-8)	1 (0-5)
Photon IFRT fields, No. (%)			
WBRT		9 (43)	
Focal spine RT		1 (5)	
WBRT + focal spine RT		8 (38)	

Abbreviations: *ALK/ROS1*+, anaplastic lymphoma kinase and c-ros oncogene 1 rearrangements; *EGFR*+, epidermal growth factor receptor gene exon 19 or L858R mutations; *HER2*+, human epidermal growth factor receptor 2 overexpression; IFRT, involved-field radiotherapy; KPS, Karnofsky performance score; MRI, magnetic resonance imaging; NSCLC, non–small-cell lung cancer; pCSI, proton craniospinal irradiation; RT, radiotherapy; SCLC, small-cell lung cancer; WBRT, whole-brain radiotherapy.

range: 0.2-18.9 months). The estimated CNS progression rates at 3 months and 6 months were 7% (95% CI, 1.2 to 20) and 21% (95% CI, 8.4 to 38), respectively. The median CNS PFS in this cohort was 5.8 months (95% CI, 4.4 to 9.1 months). Median OS was 6.6 months (95% CI, 5.4 to 11 months).

No patient experienced grade 5 toxicity. Lymphopenia was the only grade 4 TAE reported (n = 6, 17%). Grade 3 nonhematologic toxicities included headache (n = 1; 3%), muscle weakness (n = 1; 3%), nausea (n = 1; 3%), and vomiting (n = 1; 3%).

CSF CTCs

We measured baseline CSF CTC count in 36 (86%) patients in the randomized pCSI group, 17 (81%) patients in the randomized photon IFRT group, and 24 (69%) patients in the exploratory pCSI group. There was no statistically significant difference in baseline CTC count between treatment groups. For pCSI patients, baseline CTC > 136 cells/3 mL (median) was associated with worse CNS TTP (HR, 4.26; 95% CI, 1.36 to 13.4; $P = .007$), CNS PFS (HR, 2.05; 95% CI, 1.21 to 5.04; $P = .011$), and OS (HR, 2.94; 95% CI, 1.36 to 6.34; $P = .004$). For IFRT patients, baseline CTC > 199 cells/3 mL (median) was associated with worse CNS TTP (HR, 4.07; 95% CI, 1.02 to 16.27; $P = .036$) and CNS PFS (HR, 4.07; 95% CI, 1.02 to 16.27; $P = .036$), but not OS.

Numerical trends in CTC count following protocol therapy (Fig 3A) and the association with patient outcomes were investigated using joint modeling between the randomized pCSI and IFRT groups. After completion of RT, mean CTC count declined among patients treated with pCSI and increased among patients treated with IFRT (Fig 3B). For IFRT patients, the increase in CTC trend was significantly

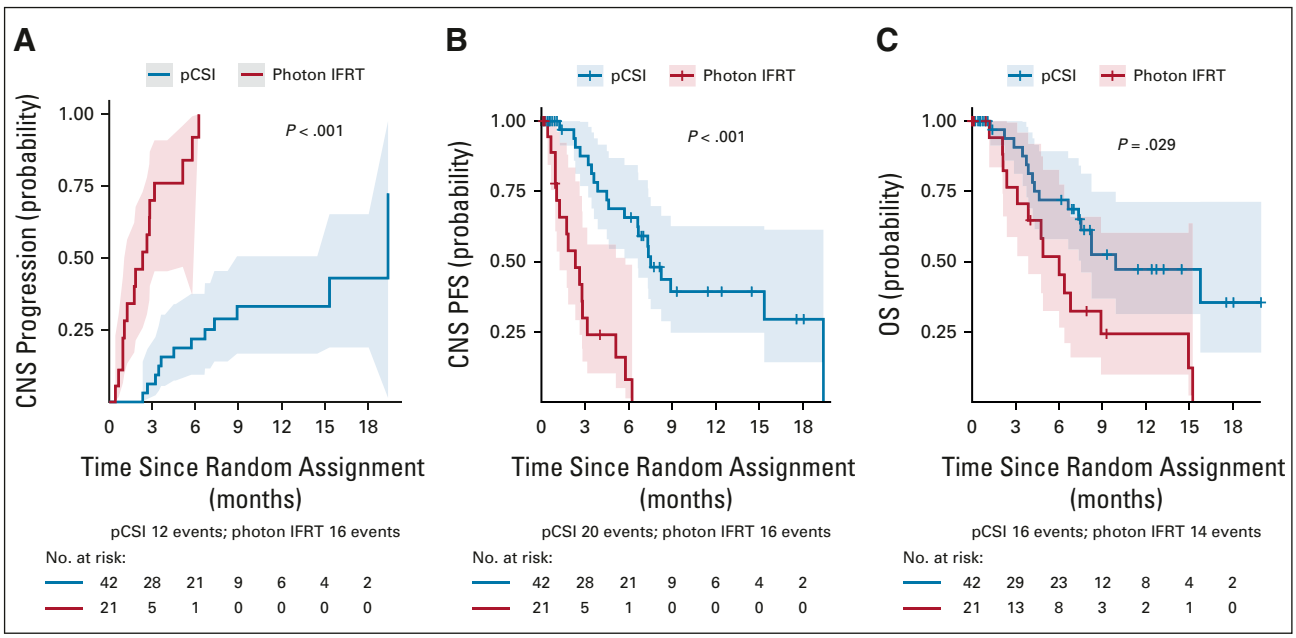

FIG 2. Patients who were randomly assigned to pCSI had significantly improved (A) CNS time to progression, (B) CNS PFS, and (C) OS. IFRT, involved-field radiotherapy; OS, overall survival; PFS, progression-free survival; pCSI, proton craniospinal irradiation.

TABLE 2. Multivariate Cox Proportional Hazard Regression With CNS PFS and OS as Outcomes

Variables	HR	95% CI	*P*
CNS PFS			
pCSI (reference: photon IFRT)	0.15	0.07 to 0.33	< .001
Stable/no systemic disease (reference: active)	0.50	0.25 to 1.00	.049
OS			
pCSI (reference: photon IFRT)	0.43	0.21 to 0.90	.025
Stable/no systemic disease (reference: active)	0.39	0.18 to 0.87	.020

Abbreviations: HR, hazard ratio; IFRT, involved-field radiotherapy; OS, overall survival; pCSI, proton craniospinal irradiation; PFS, progression-free survival.

associated with worse CNS TTP (HR, 1.23 per 10-cell increment; 95% CI, 1.14 to 1.32; $P < .001$), CNS PFS (HR, 1.24 per 10 cells; 95% CI, 1.16 to 1.32; $P < .001$), and OS (HR, 1.18 per 10 cells; 95% CI, 1.10 to 1.26; $P < .001$). Histology was not significantly associated with CTC count change over time or outcomes.

DISCUSSION

This is the first randomized trial evaluating the optimal RT for patients with solid tumor LM. CNS PFS was significantly longer for patients with NSCLC and breast cancer LM who underwent pCSI compared with standard-of-care photon IFRT, resulting in early study closure recommended by the Data and Safety Monitoring Committee. We observed prolonged OS with pCSI compared with IFRT, and that pCSI was not associated with an increase in high-grade adverse events.

RT is essential in the treatment of solid tumor LM. Photon IFRT, in the form of WBRT and/or focal spine RT, is supported by guidelines for symptomatic and bulky disease.[29,30] Several studies have supported a potential role for CSI for solid tumor LM with prolonged CNS disease control,[20,31-33] including our institutional phase I trial, which demonstrated that hypofractionated pCSI is a safe and potentially effective treatment for LM.[22] In this study, we conclude that pCSI is more efficacious than IFRT in CNS disease control, with an estimated 22% of pCSI patients and 97% of IFRT patients experiencing CNS progression at 6 months after therapy. The advantage in disease control translated into a significant improvement in CNS PFS with pCSI in patients with NSCLC and breast cancer LM (median 7.5 *v* 2.3 months with IFRT, $P < .001$). This result is comparable with our prior publications of pCSI for solid tumor LM that predominantly included patients with NSCLC or breast cancer.[22,23] For the exploratory pCSI group including patients of other solid tumor histologies, a notably shorter CNS PFS was found. Although our study was not designed to compare the exploratory group to the randomized groups, the shorter CNS PFS in the exploratory group is likely because of the higher rate of systemic disease progression-related death (31%) compared with the randomized pCSI group (19%), as the CNS control was similar at 6 months for both groups (22% *v* 21%). Whether pCSI is a potentially efficacious approach for LM of other solid tumor histologies warrants further dedicated investigation.

In addition to CNS PFS, we observed a significant OS benefit with pCSI (median 9.9 months) compared with IFRT (median 6.0 months, $P = .029$) in patients with NSCLC and breast LM. The OS advantage of pCSI is likely a direct consequence of improved CNS disease control, as 19% of pCSI patients compared with 67% of IFRT patients died with CNS progression. It is undeniable that significant strides have been made in the management of NSCLC and breast cancer CNS metastases that harbor targetable mutations, including epidermal growth factor receptor (*EGFR*) exon 19 or L858R mutations,[34,35] anaplastic lymphoma kinase and c-ros oncogene 1 (*ALK/ROS1*) rearrangements,[36,37] and human epidermal growth factor receptor 2 *(HER2)* overexpression.[12,38,39] Nevertheless, most patients in the randomized groups did not express these sensitizing mutations (52% in each group), and all patients with such mutations had received targeted therapies before trial enrollment (Table 1). As the groups were balanced and confounding factors were included in our multivariate analysis that confirmed pCSI as a prognostic factor for favorable OS, we are encouraged by this finding. Compared with patients of the randomized pCSI group, patients of the exploratory pCSI group demonstrated a shorter OS. Again, this is most likely related to the higher rate of systemic disease progression-related deaths in this group. It is difficult to conclude the effect of pCSI on OS in this heterogeneous group of patients; nevertheless, OS in this group compared favorably to recent reports of LM from gynecologic malignancies,[40] melanoma,[16] and those that include multiple histologies.[5,33,41-44]

CSF CTC count has been shown to be a valuable tool to predict survival in patients with LM.[45] In an exploratory analysis, we determined that baseline CTC count is a predictive biomarker of CNS control and survival in patients treated with pCSI, confirming our prior results.[23] Furthermore, although pCSI is associated with overall decrease in CTC count after treatment, increase in CTC count was observed after IFRT and was associated with

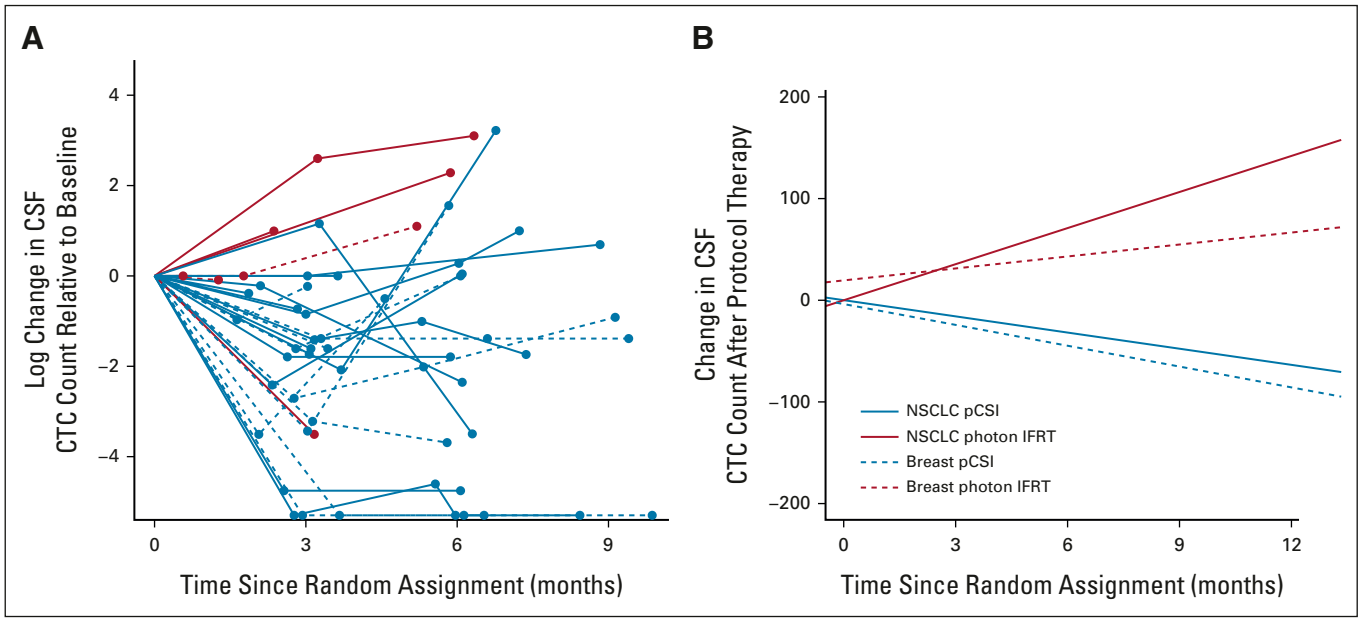

FIG 3. (A) The log CSF CTC count relative to baseline for each subject is shown over time for IFRT (red) and pCSI (blue). Patients who only had baseline CSF CTC counts are not shown. (B) Estimated effect of treatment on CSF CTC count assessed through joint modeling of longitudinal and survival outcomes with shared random effects and an unspecified baseline risk function.[23] From the linear mixed-model component of the joint model of overall survival, we reported the slope from a nonsignificant interaction between histology and treatment arm. Although pCSI was associated with a decreasing CTC count after treatment, increasing CTC count was observed after IFRT. CTC, circulating tumor cell; IFRT, involved-field radiotherapy; NSCLC, non–small-cell lung cancer; pCSI, proton craniospinal irradiation.

poorer outcomes for these patients. Our results demonstrated that comprehensive treatment of the entire leptomeningeal compartment, such as with pCSI, is needed to reduce CSF LM burden.

To our knowledge, our study represents the first prospective trial of RT for solid tumor LM, and the first randomized trial that demonstrates survival benefit in solid tumor LM using RT. However, we had a relatively small sample size resulting from early discontinuation of the trial, and the study was not powered to evaluate differences in OS. Therefore, additional investigation is required to assess the impact of pCSI on OS in this population. We also recognize that the landscape of systemic therapy is continuously changing. However, our balanced random assignment of patients would in part account for this limitation.

In summary, our randomized phase II trial provides evidence supporting pCSI treatment over standard-of-care photon IFRT in patients with NSCLC and breast cancer LM in the form of improved CNS PFS with no increase in serious toxicity. We also observed an OS improvement after pCSI, which we aim to validate through a phase III randomized trial. CSF CTC count was associated with survival outcomes.

AFFILIATIONS

[1]Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY
[2]Department of Neurology, Memorial Sloan Kettering Cancer Center, New York, NY
[3]Department of Radiology, Memorial Sloan Kettering Cancer Center, New York, NY
[4]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY
[5]Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Melanoma and Immunotherapeutics Service, New York, NY
[6]Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Thoracic Oncology Service, New York, NY
[7]Division of Solid Tumor Oncology, Department of Medicine, Memorial Sloan Kettering Cancer Center, Breast Medicine Service, New York, NY
[8]Human Oncology and Pathogenesis Program, Memorial Sloan Kettering Cancer Center, Brain Tumor Center, New York, NY

CORRESPONDING AUTHOR

Jonathan T. Yang, MD, PhD, Department of Radiation Oncology, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065; Twitter: JYangMDPhD; e-mail: jonathan.t.yang@gmail.com.

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AUTHOR CONTRIBUTIONS

Conception and design: Jonathan T. Yang, Elena Pentsova, Suzanne Wolden, Robert J. Young, Zhigang Zhang, Allison Betof Warner, Helena Yu, Mark G. Kris, Andrew D. Seidman, Andrew Lin, Lisa M. DeAngelis, Nancy Y. Lee, Simon N. Powell, Adrienne Boire
Administrative support: Alexa Steckler, Weronika Bucwinska, Ashley Bernstein
Provision of study materials or patients: Jonathan T. Yang, Elena Pentsova, Suzanne Wolden, Allison Betof Warner, Helena Yu, Mark G. Kris, Andrew D. Seidman, Jessica A. Wilcox, Rachna Malani, Andrew Lin, Lisa M. DeAngelis, Nancy Y. Lee, Simon N. Powell, Adrienne Boire
Collection and assembly of data: Jonathan T. Yang, N. Ari Wijetunga, Elena Pentsova, Suzanne Wolden, Robert J. Young, Denise Correa, Alexa Steckler, Weronika Bucwinska, Ashley Bernstein, Helena Yu, Mark G. Kris, Andrew D. Seidman, Jessica A. Wilcox, Rachna Malani, Andrew Lin, Lisa M. DeAngelis, Nancy Y. Lee, Simon N. Powell, Adrienne Boire
Data analysis and interpretation: Jonathan T. Yang, N. Ari Wijetunga, Suzanne Wolden, Robert J. Young, Denise Correa, Zhigang Zhang, Junting Zheng, Allison Betof Warner, Helena Yu, Mark G. Kris, Andrew D. Seidman, Jessica A. Wilcox, Rachna Malani, Andrew Lin, Lisa M. DeAngelis, Nancy Y. Lee, Simon N. Powell, Adrienne Boire
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Randomized Phase II Trial of Proton Craniospinal Irradiation Versus Photon Involved-Field Radiotherapy for Patients With Solid Tumor Leptomeningeal Metastasis

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Jonathan T. Yang
Stock and Other Ownership Interests: Nanocan Therapeutics
Consulting or Advisory Role: Debiopharm Group, Galera Therapeutics, AstraZeneca, Nanocan Therapeutics
Research Funding: AstraZeneca, Kazia Therapeutics, X-RAD Therapeutics

Robert J. Young
Stock and Other Ownership Interests: Agios
Consulting or Advisory Role: Agios, Puma Biotechnology, NordicNeuroLab, ICON Clinical Research, Olema Pharmaceuticals
Research Funding: Agios (Inst)

Alexa Steckler
Employment: Memorial Sloan-Kettering Cancer Center

Allison Betof Warner
Consulting or Advisory Role: Nanobiotix, Iovance Biotherapeutics, Novartis, Shanghai Jo'Ann Medical Technology, BluePath Solutions, Pfizer, Instil Bio

Helena Yu
Consulting or Advisory Role: AstraZeneca, Daiichi Sankyo, Blueprint Medicines, Janssen, C4 Therapeutics, Cullinan Oncology, Black Diamond Therapeutics
Research Funding: AstraZeneca (Inst), Astellas Pharma (Inst), Lilly (Inst), Novartis (Inst), Pfizer (Inst), Daiichi Sankyo (Inst), Cullinan Oncology (Inst), Janssen Oncology (Inst), Erasca Inc (Inst), Blueprint Medicines
Travel, Accommodations, Expenses: Lilly
Other Relationship: Astellas Pharma

Mark G. Kris
Consulting or Advisory Role: AstraZeneca, Pfizer, Janssen, Sanofi, Daiichi-Sankyo, Novartis
Travel, Accommodations, Expenses: Genentech
Open Payments Link: https://openpaymentsdata.cms.gov/physician/markgkris/summary

Andrew D. Seidman
Honoraria: Genomic Health, Lilly, Genentech/Roche, Novartis, AstraZeneca, Gilead Sciences, Pfizer, BeyondSpring Pharmaceuticals
Consulting or Advisory Role: Genentech/Roche, Novartis, Lilly, BeyondSpring Pharmaceuticals, Pfizer, Gilead/Forty Seven, Cancer Expert Now, G1 Therapeutics, Incyte, Affinia Therapeutics
Speakers' Bureau: Genomic Health, Genentech/Roche, Lilly, Novartis/Pfizer, Gilead Sciences
Research Funding: Bayer, Odonate Therapeutics (Inst), Nektar (Inst)

Andrew Lin
Stock and Other Ownership Interests: Novo Nordisk, Dexcom, Tandem Diabetes Care, Amedisys, Abbott Laboratories, Atea
Research Funding: Bristol Myers Squibb

Lisa M. DeAngelis
Consulting or Advisory Role: Sapience Therapeutics

Nancy Y. Lee
Consulting or Advisory Role: Merck, Pfizer, Merck Serono, Sanofi, Mirati Therapeutics, Roche/Genentech
Research Funding: AstraZeneca, Pfizer (Inst)

Simon N. Powell
Consulting or Advisory Role: Varian Medical Systems, Philips Healthcare, Rain Therapeutics
Research Funding: Philips Healthcare, Varian Medical Systems

Adrienne Boire
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APPENDIX

TABLE A1. Normal Tissue Constraints for Proton Craniospinal Irradiation

		Total Dose From All Treatments		
OAR	**Normal Organ Tolerances**	**All Prescription, Gy (RBE)**	**≤ 60 Gy (RBE)**	**> 60 Gy (RBE)**
Spinal cord	Dose to 0.1 cc		< 50 Gy (RBE)	
	Core max			53 Gy (RBE)
	Surface max			64 Gy[a] (RBE)
Cauda equina	Dose to 0.1 cc		< 50 Gy (RBE)	64 Gy (RBE)
Optic chiasm	Dose to 0.05 cc		≤ 54 Gy (RBE)	
				≤ 60 Gy (RBE)
	Mean dose			≤ 58 Gy (RBE)
	1/3 OAR limit rule: only one of three OARs (R optic nerve, L optic nerve, or optic chiasm) can receive this dose			
Optic nerve	Dose to 0.05 cc		≤ 54 Gy (RBE)	
	Dose to 0.05 cc			≤ 60 Gy[a] (RBE)
	1/3 OAR limit rule: only one of three OARs (R optic nerve, L optic nerve, or optic chiasm) can receive this dose			
Brainstem	Dose to 0.05 cc		< 60 Gy (RBE)	
	Core max dose			53 Gy (RBE)
	Surface max dose			64 Gy[a] (RBE)
	Brainstem core—defined as 3-mm diameter central structure within brainstem			
Cochlea	Mean dose	< 45 Gy (RBE)		
	If absent ipsilateral hearing; contralateral constraint < 35 CGE *If high target/tumor dose and bilateral hearing, this is a guideline only and should not affect ipsilateral target coverage*			
Esophagus	Mean dose	< 40 Gy (RBE)		
	Max dose	< Rx dose		
	V60 Gy	< 17%		
Heart	V5 Gy	< 40%		
	V20 Gy	< 20%		
	V30 Gy	< 50%		
	V45 Gy	< 35%		
	Mean dose	< 35 Gy (RBE)		
Lung	Lung total	V20 Gy	< 35%	
	Lung total	V10 Gy	< 40%	
	Lung total	V5 Gy	< 60%	
	Lung total	Mean	< 20 Gy (RBE)	
	L/R lung	V20 Gy	< 15%	
Lung	L/R lung	V5 Gy	< 20%	
Kidney	V18 Gy	< 33%		
Bowel	Bowel 1.0 cc		< 55 Gy (RBE)	≤ 60 Gy (RBE)
	Bowel 0.03 cc			≤ 64 Gy (RBE)
Stomach	Max dose	< 58 Gy (RBE)		
	V70 Gy	< 25%		

NOTE. All doses are in 2 Gy EQD (equivalent dose in 2 Gy fractions; a/b = 2).
Abbreviations: CGE, cobalt gray equivalent; Gy (RBE), gray (relative biological effectiveness); L, left; OAR, organ at risk; R, right; V, volume.
[a]Isodose line may touch surface.

TABLE A2. Protocol Therapy–Related AEs (TAEs)

AEs	Randomized pCSI Group, No. (%)	Randomized Photon IFRT Group, No. (%)	Exploratory pCSI Group, No. (%)
Nonhematologic TAEs			
Blurred vision			
Grade 1	4 (10)	2 (10)	1 (3)
Grade 2			1 (3)
Cognitive disturbance			
Grade 1	1 (2)		
Concentration impairment			
Grade 1	1 (2)		3 (9)
Dermatitis			
Grade 1	1 (2)		3 (9)
Grade 2	1 (2)		
Diarrhea			
Grade 1		2 (10)	
Grade 2	1 (2)		
Dizziness			
Grade 1	2 (5)	3 (14)	1 (3)
Dry mouth			
Grade 1	5 (12)		2 (6)
Grade 2	2 (5)		2 (6)
Dysgeusia			
Grade 2	1 (2)		
Fatigue			
Grade 1	1 (2)	2 (10)	4 (11)
Grade 2	9 (21)	1 (5)	5 (15)
Grade 3	1 (2)	2 (10)	
Gait disturbance			
Grade 1	3 (7)		2 (6)
Grade 2	3 (7)	2 (10)	
Grade 3		1 (5)	
Headache			
Grade 1	5 (12)	3 (14)	5 (14)
Grade 2	2 (5)	1 (5)	1 (3)
Grade 3		1 (5)	1 (3)
Hearing impairment			
Grade 1	1 (2)		1 (2)
Grade 2		1 (5)	
Muscle weakness			
Grade 1	3 (7)		
Grade 2	5 (12)	4 (19)	1 (3)
Grade 3			1 (3)
Nausea			
Grade 1	6 (14)	3 (14)	6 (17)
Grade 2	2 (5)		
Grade 3			1 (3)

(continued on following page)

TABLE A2. Protocol Therapy–Related AEs (TAEs) (continued)

AEs	Randomized pCSI Group, No. (%)	Randomized Photon IFRT Group, No. (%)	Exploratory pCSI Group, No. (%)
Pain			
Grade 1	7 (17)	5 (24)	4 (11)
Grade 2	2 (5)		1 (3)
Grade 3	1 (2)		
Paresthesia			
Grade 1	1 (2)		1 (3)
Seizure			
Grade 1	1 (2)		
Grade 2			1 (3)
Vomiting			
Grade 1	2 (5)	1 (5)	3 (9)
Grade 2	1 (2)		
Grade 3	1 (2)		1 (3)
Hematologic TAEs			
Anemia			
Grade 1	9 (21)	8 (38)	8 (23)
Grade 2	4 (10)	3 (14)	3 (9)
Grade 3			1 (3)
Leukopenia			
Grade 1	1 (2)		5 (14)
Grade 2	8 (19)		5 (14)
Grade 3			1 (3)
Lymphopenia			
Grade 1	2 (5)	1 (5)	3 (9)
Grade 2	6 (14)	2 (10)	8 (23)
Grade 3	23 (55)	9 (43)	12 (34)
Grade 4	4 (10)	4 (19)	6 (17)
Neutropenia			
Grade 1		5 (24)	
Grade 2	2 (5)		1 (3)
Grade 3	1 (2)		1 (3)
Thrombocytopenia			
Grade 1	20 (48)		18 (51)
Grade 2	2 (5)		1 (3)
Grade 3	1 (2)		

Abbreviations: AE, adverse event; IFRT, involved-field radiotherapy; pCSI, proton craniospinal irradiation; TAE, treatment-related adverse event.