original report

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

Daniel R. Gomez, MD[1]; Chad Tang, MD[1]; Jianjun Zhang, MD, PhD[1]; George R. Blumenschein Jr, MD[1]; Mike Hernandez, MS[1]; J. Jack Lee, PhD[1]; Rong Ye, MS[1]; David A. Palma, MD, PhD[2]; Alexander V. Louie, PhD, MSc[2]; D. Ross Camidge, MD, PhD[3]; Robert C. Doebele, MD, PhD[3]; Ferdinandos Skoulidis, MD, PhD[1]; Laurie E. Gaspar, MD[3]; James W. Welsh, MD[1]; Don L. Gibbons, MD[1]; Jose A. Karam, MD[1]; Brian D. Kavanagh, MD, MPH[3]; Anne S. Tsao, MD[1]; Boris Sepesi, MD[1]; Stephen G. Swisher, MD[1]; and John V. Heymach, MD, PhD[1]

abstract

PURPOSE Our previously published findings reported that local consolidative therapy (LCT) with radiotherapy or surgery improved progression-free survival (PFS) and delayed new disease in patients with oligometastatic non–small-cell lung cancer (NSCLC) that did not progress after front-line systemic therapy. Herein, we present the longer-term overall survival (OS) results accompanied by additional secondary end points.

PATIENTS AND METHODS This multicenter, randomized, phase II trial enrolled patients with stage IV NSCLC, three or fewer metastases, and no progression at 3 or more months after front-line systemic therapy. Patients were randomly assigned (1:1) to maintenance therapy or observation (MT/O) or to LCT to all active disease sites. The primary end point was PFS; secondary end points were OS, toxicity, and the appearance of new lesions. All analyses were two sided, and *P* values less than .10 were deemed significant.

RESULTS The Data Safety and Monitoring Board recommended early trial closure after 49 patients were randomly assigned because of a significant PFS benefit in the LCT arm. With an updated median follow-up time of 38.8 months (range, 28.3 to 61.4 months), the PFS benefit was durable (median, 14.2 months [95% CI, 7.4 to 23.1 months] with LCT *v* 4.4 months [95% CI, 2.2 to 8.3 months] with MT/O; *P* = .022). We also found an OS benefit in the LCT arm (median, 41.2 months [95% CI, 18.9 months to not reached] with LCT *v* 17.0 months [95% CI, 10.1 to 39.8 months] with MT/O; *P* = .017). No additional grade 3 or greater toxicities were observed. Survival after progression was longer in the LCT group (37.6 months with LCT *v* 9.4 months with MT/O; *P* = .034). Of the 20 patients who experienced progression in the MT/O arm, nine received LCT to all lesions after progression, and the median OS was 17 months (95% CI, 7.8 months to not reached).

CONCLUSION In patients with oligometastatic NSCLC that did not progress after front-line systemic therapy, LCT prolonged PFS and OS relative to MT/O.

J Clin Oncol 37:1558-1565. © 2019 by American Society of Clinical Oncology

ASSOCIATED CONTENT

Appendix

Data Supplements

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on March 19, 2019 and published at jco.org on May 8, 2019: DOI https://doi.org/10.1200/JCO.19.00201

INTRODUCTION

Oligometastatic cancer continues to be defined biologically,[1,2] and the roles of radiation therapy and surgery have evolved substantially during the past decade. In patients with these cancers, it is technically feasible to use definitive radiation therapy or surgical therapy to control all known sites of disease, termed local consolidative therapy (LCT). The notion that LCT could improve progression-free survival (PFS) has been suggested from retrospective and single-arm prospective studies and, more recently, from five prospective randomized studies (two in lung cancer,[3,4] one in prostate cancer,[5] one in colorectal cancer,[6] and one in multiple histology[7]). Other ongoing trials are addressing this issue, but to date no randomized clinical trials have demonstrated an overall survival (OS) benefit from LCT in patients with lung cancer.

We conducted and subsequently published the findings from a multi-institutional, randomized study that examined the efficacy of LCT on PFS in oligometastatic non–small cell-lung cancer (NSCLC) in 2016.[4] The trial was closed early after it demonstrated an observed

8-month benefit in PFS for patients who received LCT relative to patients who received maintenance therapy or observation (MT/O); the median PFS was 11.9 months in the LCT arm (90% CI, 5.72 to 20.90 months) versus 3.9 months in the MT/O arm (log-rank $P = .005$). The aims of this paper were to present final PFS data for these patients and to report OS outcomes, with supplementary analyses used to generate hypotheses about the biologic basis for the effects of LCT on these patients. The exploratory analyses also allowed us to assess differences in OS outcomes after early (initial) versus late (after progression) LCT.

PATIENTS AND METHODS

Study Design

Although the details of the study design and statistical methods have been previously published,[4] this is a brief summary: Three institutions contributed patients to this study (MD Anderson Cancer Center, Houston, TX; London Health Sciences Center, London, Ontario; and The University of Colorado, Aurora, CO), and all three sites approved the study. Eligible patients (1) had pathologically confirmed NSCLC, (2) had stage IV disease according to the seventh edition of the American Joint Committee on Cancer staging system, (3) had three or fewer metastases, not including the primary tumor, (4) had an Eastern Cooperative Oncology Group performance status of 2 or less, (5) were age 18 years or older, and (6) received standard front-line systemic therapy. This standard therapy was defined as (1) at least four cycles of platinum doublet chemotherapy, (2) erlotinib or another approved first-line epidermal growth factor receptor tyrosine kinase inhibitor for at least 3 months for tumors with known *EGFR* mutations, or (3) crizotinib for at least 3 months for tumors with an anaplastic lymphoma kinase rearrangement.

Treatment

Patients were randomly assigned either to LCT with radiation therapy or surgery followed by standard maintenance or observation (LCT arm) or to standard maintenance or observation (MT/O arm). Maintenance therapy was chosen by the treating physician from a predefined set of standard-of-care options. The random assignment was not masked to the patients or study team.

In lieu of stratification, the random assignment was balanced dynamically on five prognostic covariables related to PFS,[8] namely number of metastatic disease sites (0–1 *v* 2 to 3); response to first-line systemic therapy (stable disease *v* partial response); CNS metastases (yes *v* no); (d) intrathoracic nodal status (N0/N1 *v* N2/N3), and *EGFR*/*ALK* mutation (yes *v* no). The choice of LCT (surgery *v* radiation) was made by a multidisciplinary treatment team.[4] Although patients with a complete response were not eligible for random assignment, those with a complete response in the metastatic sites and a persistent primary tumor could remain in the study and were considered to have zero metastatic sites. Patients in the MT/O arm were allowed to cross over at the time of progression and receive LCT.

Outcomes and Statistical Analyses

The primary outcome, PFS, was defined from the time of random assignment to the time of disease progression or death, whichever occurred first. To evaluate this end point, radiographic evaluations were conducted at follow-up intervals of every 8 ± 2 weeks, regardless of the treatment arm. To avoid introduction of a delay in follow-up imaging for patients in the LCT arm, the protocol was intentionally designed to index all imaging to the date of enrollment and to not deviate from this calendar during local therapy. Secondary outcomes were OS, safety and tolerability (ie, toxicity), and time to new lesion progression. OS was defined from the time of random assignment to death or, for alive patients, the date of last contact. Time to new lesion progression from the time of random assignment was compared between treatment groups using log-rank tests. Findings for quality of life were insufficient to report.

The trial used a one-sided 10% type I error and had 90% power to detect an improvement in PFS from 4 months in the standard of care MT/O arm (chosen on the basis of prior studies of maintenance therapy[9-13]) to 7 months in the experimental LCT arm, which corresponded to a hazard ratio (HR) of 0.57 or a 75% improvement in median PFS. In view of these assumptions, the design was powered for 94 patients to be randomly assigned in 37.6 months with an additional 9 months of follow-up. PFS, the appearance of new lesions, and OS were compared between the LCT and MT/O arms with log-rank tests and an intent-to-treat analysis. The log-rank test was used to compare survival distributions between treatment arms.[14]

Late LCT was defined as definitive LCT to all radiographically visible disease sites at the time of progression. Two additional exploratory analyses were done to assess OS after progression, using progression date as the index date and stratified by randomly assigned arm and receipt of late LCT. Notably, in both of these exploratory analyses, the three patients in the MT/O arm who crossed over to receive LCT before progression were excluded. We excluded these patients because, given that crossover and LCT receipt occurred before progression, they did not adhere to either arm and did not receive either early (after front-line therapy) or late (at the time of progression) LCT per our definitions.

Next, we analyzed the association of OS with major clinical variables of interest on which random assignment was

balanced: (1) number of metastases (0 to 1 *v* 2 to 3), (2) response to first-line chemotherapy (stable disease *v* partial response), (3) CNS metastases (no *v* yes), (4) nodal status (N0/N1 *v* N2/N3), and (5) *EGFR*/*EML4ALK* status (none *v EGFR*/*EML4ALK*). Finally, we fit a multivariable model that included treatment arm and the above clinical variables that were most strongly correlated with OS, and we incorporated one variable for every 10 events (eg, deaths) in the trial to reduce the chance of overfitting data.

TABLE 1. Patient Characteristics

Characteristic	No. (%) of Patients		
	LCT (n = 25)	No LCT (n = 24)	Total (N = 49)
Age, years			
Mean ± standard deviation	64 ± 10	63 ± 10	63 ± 10
Median (range)	63 (43-83)	61 (43-80)	61 (43-83)
Sex			
Male	12 (48)	10 (42)	22 (45)
Female	13 (52)	14 (58)	27 (55)
Ethnicity			
White	20 (80)	18 (75)	38 (78)
Black	2 (8)	3 (12)	5 (10)
Hispanic	2 (8)	0 (0)	2 (4)
Asian	1 (4)	3 (12)	4 (8)
Tumor histology			
Adenocarcinoma	21 (84)	18 (75)	39 (80)
Adenosquamous	0 (0)	1 (4)	1 (2)
NSCLC, NOS	1 (4)	0 (0)	1 (2)
Poorly differentiated NSCLC, NOS	2 (8)	0 (0)	2 (4)
SCC	1 (4)	4 (17)	5 (10)
Sarcomatoid carcinoma	0 (0)	1 (4)	1 (2)
Timing of metastatic disease			
Metachronous	1 (4)	2 (8)	3 (6)
Synchronous	24 (96)	22 (92)	46 (94)
No. of nonregional metastases after initial systemic therapy			
0-1	17 (68)	15 (62)	32 (65)
2-3	8 (32)	9 (38)	17 (35)
Response to first-line chemotherapy			
PR/CR	9 (36)	9 (38)	18 (37)
SD	16 (64)	15 (62)	31 (63)
CNS metastases			
No	18 (72)	18 (75)	36 (73)
Yes	7 (28)	6 (25)	13 (27)
Nodal status			
N0/N1	12 (48)	11 (46)	23 (47)
N2/N3	13 (52)	13 (54)	26 (53)
Mutation type			
None	20 (80)	21 (88)	41 (84)
EGFR	3 (12)	3 (12)	6 (12)
EML4ALK	2 (8)	0 (0)	2 (4)

Abbreviations: LCT, local consolidative therapy; NSCLC, non–small-cell lung cancer; NOS, not otherwise specified; SCC, squamous cell carcinoma; PR, partial response; CR, complete response; SD, stable disease.

RESULTS

As noted in our initial publication, the trial was closed early after a planned annual Data Safety Monitoring Board analysis revealed that, according to the data at that time, there was a 99.46% probability of superiority of the LCT arm if the current trend continued. Of the 74 patients enrolled on the trial at the time of closure, 49 (66%) were randomly assigned and included in this analysis. Patient characteristics have been previously published and are listed in Table 1. Treatment regimens also have been previously published and are listed in Appendix Table A1 (online only). Note that the LCT regimens could include surgery, radiation, or a combination of the two. Concurrent chemoradiation also was allowed for the primary tumor and regional lymph nodes. The median follow-up time for censored patient data at the date the patient was last known to be alive was 38.8 months (range, 28.3 to 61.4 months). Thirty-nine patients were identified as having progression (19 of 25 in the LCT group and 20 of the 24 in the MT/O group), and three patients in the MT/O arm had their data censored, because they received upfront LCT before disease progression. The median PFS time for all patients was 8.3 months (95% CI, 5.2 to 14.2 months). The previously noted PFS benefit from LCT was maintained; the median PFS was 14.2 months in the LCT group (95% CI, 7.4 to 23.1 months) versus 4.4 months in the MT/O group (95% CI, 2.2 to 8.3 months; P = .022; Fig 1A). The median time to appearance of new lesions was 14.2 months in the LCT group (95% CI, 5.7 to 24.3 months) versus 6.0 months in the MT/O group (95% CI, 4.4 to 8.3 months; P = 0.11).

Twenty-nine of the original 49 patients died by the time of this analysis: 11 of 25 died in the LCT group, and 18 of 24 died in the MT/O group. The median OS time for all patients was 37.7 months (95% CI, 16.6 to 41.2 months). OS time was significantly longer in the LCT group (median, 41.2 months; 95% CI, 18.9 months to not reached) than in the MT/O group (median, 17.0 months; 95% CI, 10.1 to 39.8 months; P = .017; Fig 1B).

Salvage therapies for all patients included additional systemic therapy, LCT to all progressing sites of disease, and combinations thereof (Appendix Table A2, online only) on or off a clinical trial. The median survival-after-progression time for all patients was 13.6 months (95% CI, 8.4 to 37.6 months). χ^2 tests revealed no difference in the proportions of patients who received late LCT in the LCT versus MT/O group (P = .39). However, patients in the LCT group survived longer after progression relative to patients in the MT/O group (37.6 months [95% CI, 9.0 months to not reached] *v* 9.4 months [95% CI, 5.9 to 19.6 months]; P = .034; Fig 2).

Of the 39 patients who experienced progression, 15 (41%; n = 6 in the LCT group and n = 9 in the MT/O group) received LCT at the time of progression. Reasons for not undergoing LCT at the time of progression in the MT/O arm were polymetastatic progression (n = 7), poor performance status (n = 3), and refusal of radiation therapy (n = 1). Calculated from the time of progression, patients who received LCT at progression had a median OS time that was not reached (95% CI, 11.5 months to not reached) versus 16.4 months without late LCT (95% CI, 8.7 to 40.9 months; P = .119; Fig 3). In a multivariable Cox model analysis that assessed OS and incorporated both initial treatment assignment (LCT *v* MT/O) and late LCT (yes *v* no), both initial (HR, 0.30; 95% CI, 0.12 to 0.75) and late (HR, 0.44; 95% CI, 0.18 to 1.06; P = .064) treatment with LCT correlated with improved OS.

When the effect of other major clinical variables was assessed, OS was associated with two to three metastases (HR, 1.65; P = .208), partial response to first-line

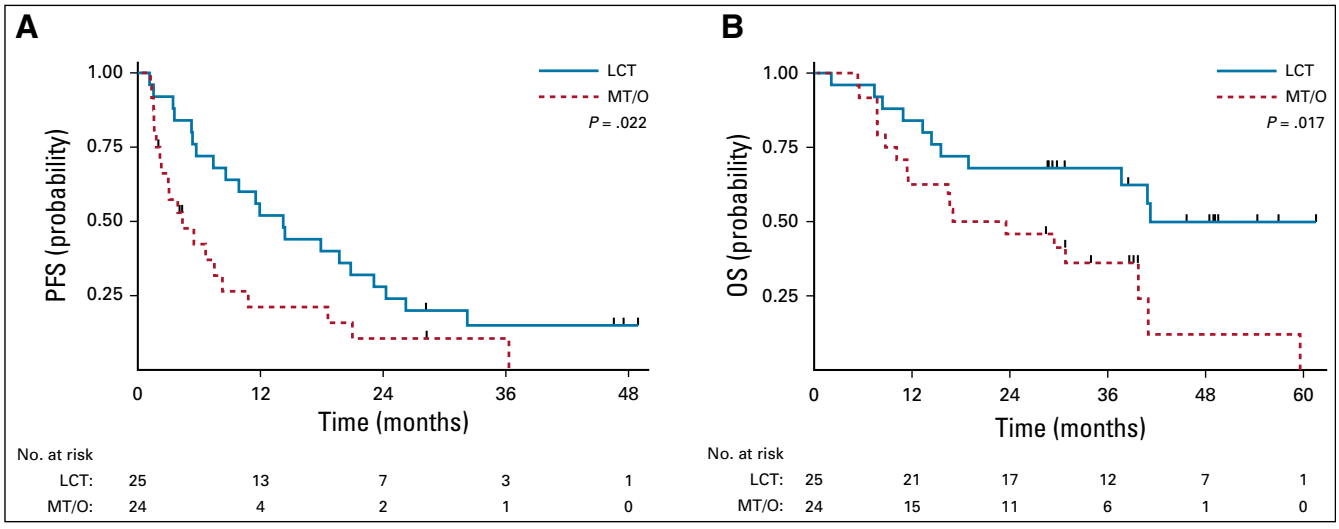

FIG 1. (A) Progression-free survival (PFS) and (B) overall survival (OS) in patients given local consolidative therapy (LCT) or maintenance therapy or observation (MT/O) for oligometastatic non–small-cell lung cancer.

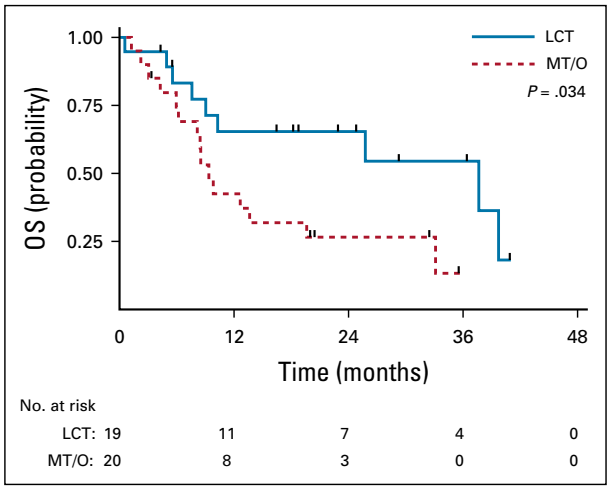

FIG 2. Overall survival (OS) after disease progression among patients originally assigned to local consolidative therapy (LCT) or maintenance therapy or observation (MT/O).

chemotherapy (HR, 1.35; $P = .452$), N2/N3 disease (HR, 1.33; $P = .443$), and CNS metastases (HR, 1.01; $P = .979$). However, none of these associations were statistically significant. Conversely, *EGFR/EML4ALK* status was correlated with a reduced risk of death (HR, 0.12; $P = .041$). Because of the small size of the *EGFR/EML4ALK* patient cohort (n = 8), additional exploratory assessments with *EGFR/EML4ALK* status were not considered. However, to better assess the effect of the treatment arm in the presence of potentially prognostic features, a multivariable model was fitted with the two clinical covariables that demonstrated the strongest association with OS: number of metastases and *EGFR/EML4ALK* alterations. In this model, the LCT arm remained associated with improved OS (HR, 0.46; 95% CI, 0.21 to 0.99; $P = .048$; Table 2). Finally, with regard to toxicity, no patient experienced any severe (grade ≥ 3) toxicity event aside from those reported previously.[4]

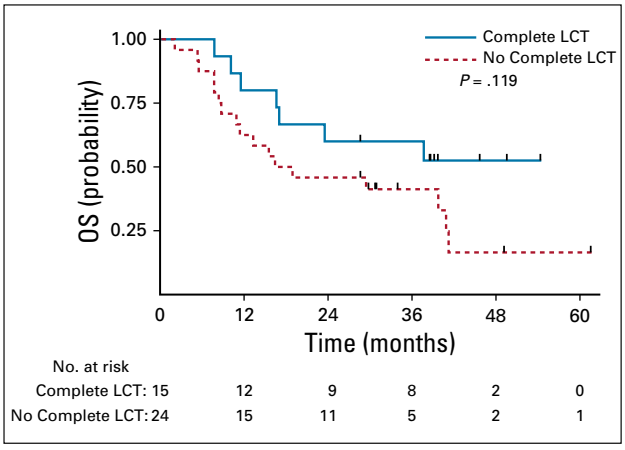

FIG 3. Overall survival (OS) from time of progression, for patients who did or did not receive late local consolidation therapy (LCT) for that progression. "Complete" LCT designates radiation therapy or surgery to all active sites of disease at the time of progression.

DISCUSSION

Our previously published findings, to our knowledge, represent the first multicenter, randomized trial of LCT for selected oligometastatic NSCLC (three or fewer metastatic lesions, no progression after front-line systemic therapy) to demonstrate that aggressive consolidation therapy led to a PFS benefit. These updated PFS and OS findings provide evidence that the PFS benefit was durable and that patients who received LCT immediately after front-line systemic therapy had better OS than did patients who received MT/O. Two features of these new results are particularly notable: (1) the median OS time in the LCT group, 41.2 months, was markedly longer than previously reported for metastatic NSCLC, particularly in the preimmunotherapy era; and (2) an OS benefit in the group originally assigned to receive LCT was observed despite allowance for patients to cross over from the MT/O arm to the LCT arm at the time of progression.

To explore possible reasons for these findings, we assessed the effects of salvage therapy after progression in both treatment groups. Two findings emerged from these analyses: (1) survival after progression was substantially longer in the LCT group; and (2) patients who received late LCT at the time of progression exhibited long OS (median OS not reached), although only 41% of patients who experienced progression received this treatment. Put another way, early LCT is better than no LCT, but late LCT at progression, if feasible, may improve OS to an extent that partly compensates for this difference. These results also imply that a primary risk of reserving LCT until progression (late LCT) is that definitive treatment to all sites of disease can be achieved in only a subset of patients.

Several potential mechanisms may explain the benefit from LCT in terms of OS and survival after progression. First, initial systemic therapy that leads to stable or responsive disease leaves behind treatment-resistant malignant cells that are less likely to be eliminated by subsequent maintenance therapy and could serve as a source for subsequent metastatic spread, even in the absence of radiographic progression. In that case, LCT would reduce the burden of treatment-resistant cells. Thus, in this scenario, delaying LCT to the time of radiographic progression would be less effective than early LCT, because it would not address distant micrometastatic disease that developed during maintenance therapy.[15,16] Second, LCT may potentiate the effects of systemic therapy; for example, consolidative radiotherapy could render residual disease more sensitive to subsequent maintenance therapy. A third possibility is that residual tumor after initial systemic therapy promotes the growth of distant micrometastatic

TABLE 2. Summary of Multivariable Cox Proportional Hazards Model That Includes Treatment Arm, Number of Metastases, and *ALK*/*EGFR* Alteration

Variable	HR	95% CI	*P*
Treatment			
MO	Ref		
LCT	0.46	(0.21 to 0.99)	.048
No. of metastases			
1	Ref		
2-3	1.50	(0.69 to 3.26)	.310
Mutation status			
None	Ref		
EGFR/*EML4ALK*	0.15	(0.02 to 1.12)	.065

Abbreviations: HR, hazard ratio; MO, maintenance therapy or observation; Ref, reference; LCT, local consolidative therapy.

disease, for example, via immunosuppressive or proangiogenic effects, as observed in preclinical models.[17] In that case, by reducing the residual tumor burden, LCT would also slow the growth of distant micrometastatic disease. Notably, these mechanisms are not mutually exclusive, and more than one could contribute to the benefits of LCT.

The OS time observed after initial LCT in this study was impressive, even in the context of other studies of consolidative therapy and before the inclusion of immunotherapy in standard treatment of NSCLC. For example, a propensity score-matched analysis of patients treated with comprehensive LCT for oligometastatic NSCLC demonstrated an OS time of 27.1 months for patients given LCT.[18] In a recent single-arm, prospective study of 29 patients given consolidative radiation therapy for oligometastatic NSCLC after three to six cycles of platinum-based chemotherapy, the median OS time was 28.4 months (95% CI, 14.5 to 45.8 months).[19] The eight patients in this study who had *EGFR* or *ALK* mutations exhibited long survival times (median PFS, 23.1 months, and median OS, not reached). These survival times are similar to, or longer than, recent reports of consolidative LCT for NSCLC with *EGFR* activating mutations. One such study recently found that OS time after LCT to all sites was 40.9 months relative to 30.8 months without any ablative therapy.[20] However, given the small number of patients in this category, the utility of LCT for NSCLC with epidermal growth factor receptor or anaplastic lymphoma kinase tyrosine kinase inhibitors merits additional investigation; we are currently enrolling patients to a randomized, phase II study of osimertinib with or without LCT for stage IV NSCLC to address this issue (ClinicalTrials.gov identifier: NCT03410043).

These results are subject to several limitations. First, and most notably, as discussed previously,[4] early closure of the trial because of efficacy resulted in the random assignment of only 49 patients, which substantially limits subgroup analyses. We attempted to account for imbalances in patient characteristics through our approach of balanced random assignment, which considered major prognostic factors (number of disease sites, response to first-line systemic therapy, presence of CNS metastases, intrathoracic nodal status, and presence of *EGFR* or *ALK* mutation). However, we intend the subset analyses of this study to be provocative and supplementary rather than paradigm shifting. Second, the front-line and maintenance systemic therapies used were somewhat heterogeneous, although all were considered standard-of-care regimens in the United States at the time of the study. Conceivably, then, the effect of LCT could differ depending on the systemic therapy used, a possibility that would be difficult to detect given the modest size of some of the subgroups. Finally, because our trial opened in 2012, it did not include immunotherapy, which has revolutionized the treatment of both locally advanced and metastatic NSCLC during the past 5 years. Thus, the use of LCT needs additional assessment in this context.

In summary, this multicenter, phase II, randomized study showed that LCT improves both PFS and OS among patients with oligometastatic NSCLC that does not progress after front-line systemic therapy. Patients originally assigned to LCT had prolonged OS times (median OS, 41.2 months) and durable survival after progression (37.6 months). These results build on our prior report by demonstrating that benefits of LCT extend beyond delay of initial progression. Overall, this study provides randomized OS data in support of the integration of LCT for patients with oligometastatic disease. However, although these data are compelling, given the limitations expressed in this Discussion, we emphasize that future studies should be supported to definitively assess the role of LCT in larger populations (eg, phase III trials such as NRG-LU002) and in the context of novel systemic therapies. Furthermore, at this time, given the restrictions of the subset analyses performed in this study, we would support an oligometastatic definition that is consistent with the inclusion criteria of this trial and with the vast majority of patients enrolled in Stereotactic Ablative Radiation Therapy for the Comprehensive Treatment of Oligometastatic Tumors (SABR-COMET)[7] and the UT Southwestern[3] randomized, phase II studies: zero to three metastases and unconstrained by molecular profile/mutational status. Note that, although these two trials allowed enrollment of patients with up to five metastases, most patients enrolled had three or fewer metastases. Our proposed definition will likely continue to evolve as the benefit of aggressive treatment is better elucidated in specific patient subgroups and through both clinical and correlative investigations.

AFFILIATIONS

[1]The University of Texas MD Anderson Cancer Center, Houston, TX
[2]London Health Sciences Center, London, Ontario, Canada
[3]University of Colorado School of Medicine, Aurora, CO

CORRESPONDING AUTHOR

Daniel R. Gomez, MD, Department of Radiation Oncology, Unit 1422, The University of Texas MD Anderson Cancer Center, 1400 Pressler St, Houston, TX 77030-4008; e-mail: gomezd@mskcc.org.

EQUAL CONTRIBUTION

S.G.S. and J.V.H. contributed equally as co-senior authors of this paper.

PRIOR PRESENTATION

Presented in part at the American Society of Radiation Oncology Meeting, San Antonio, TX, October 20-24, 2018.

SUPPORT

Supported by the MD Anderson Lung Cancer Priority Fund, the MD Anderson Cancer Center Moon Shot Initiative, The Mohaymen Sahebzadah Family Philanthropic Grant, and Cancer Center Support (Core) Grant No. CA016672 from the National Cancer Institute, National Institutes of Health.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JCO.19.00201.

AUTHOR CONTRIBUTIONS

Conception and design: Daniel R. Gomez, Mike Hernandez, J. Jack Lee, D. Ross Camidge, Stephen G. Swisher, John V. Heymach

Collection and assembly of data: Daniel R. Gomez, Chad Tang, Jianjun Zhang, Mike Hernandez, David A. Palma, Alexander V. Louie, Robert C. Doebele, Laurie E. Gaspar, James W. Welsh, Jose A. Karam, Brian D. Kavanagh, Anne S. Tsao, Boris Sepesi, Stephen G. Swisher, John V. Heymach

Provision of study material or patients: David A. Palma, D. Ross Camidge, Robert C. Doebele, Don L. Gibbons, Jose A. Karam, Anne S. Tsao, Boris Sepesi

Data analysis and interpretation: Daniel R. Gomez, Chad Tang, Jianjun Zhang, George R. Blumenschein Jr, Mike Hernandez, J. Jack Lee, Rong Ye, David A. Palma, Alexander V. Louie, D. Ross Camidge, Robert C. Doebele, Ferdinandos Skoulidis, Laurie E. Gaspar, James W. Welsh, Don L. Gibbons, Jose A. Karam, Brian D. Kavanagh, Anne S. Tsao, Boris Sepesi, Stephen G. Swisher, John V. Heymach

Manuscript writing: All authors

Final approval of manuscript: All authors

Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

We thank Suja Koshy, RN, Denise Erdman, RN, Monica Robischon, RN, Albert Gratton, Qiuling Shu, Rensi Zacharia, MD, and Monica Ramirez for their research support on the trial; Tommy Sheu, MD, for publication support; and Christine Wogan, MS, ELS, of MD Anderson's Division of Radiation Oncology, for editorial contributions. We also acknowledge the generous philanthropic contributions to the University of Texas MD Anderson Lung Cancer Priority Fund, the Mohaymen Sahebzadah Family Philanthropic Fund, and the MD Anderson Cancer Center Moon Shots Program.

REFERENCES

1. Weichselbaum RR, Hellman S: Oligometastases revisited. Nat Rev Clin Oncol 8:378-382, 2011
2. Hellman S, Weichselbaum RR: Oligometastases. J Clin Oncol 13:8-10, 1995
3. Iyengar P, Wardak Z, Gerber DE, et al: Consolidative radiotherapy for limited metastatic non–small-cell lung cancer: A phase 2 randomized clinical trial. JAMA Oncol 4:e173501, 2018
4. Gomez DR, Blumenschein GR, Jr, Lee JJ, et al: Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non–small-cell lung cancer without progression after first-line systemic therapy: A multicentre, randomised, controlled, phase 2 study. Lancet Oncol 17: 1672-1682, 2016
5. Ost P, Reynders D, Decaestecker K, et al: Surveillance or metastasis-directed therapy for oligometastatic prostate cancer recurrence: A prospective, randomized, multicenter phase II trial. J Clin Oncol 36:446-453, 2018
6. Ruers T, Van Coevorden F, Punt CJ, et al: Local treatment of unresectable colorectal liver metastases: Results of a randomized phase II trial. J Natl Cancer Inst 109:109, 2017
7. Palma DA, Olson RA, Harrow S, et al: Stereotactic ablative radiation therapy for the comprehensive treatment of oligometastatic tumors (SABR-COMET): Results of a randomized trial. Int J Radiat Oncol Biol Phys 102:S3-S4, 2018
8. Pocock SJ, Simon R: Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. Biometrics 31:103-115, 1975
9. Patel JD, Hensing TA, Rademaker A, et al: Phase II study of pemetrexed and carboplatin plus bevacizumab with maintenance pemetrexed and bevacizumab as first-line therapy for nonsquamous non–small-cell lung cancer. J Clin Oncol 27:3284-3289, 2009
10. Ciuleanu T, Brodowicz T, Zielinski C, et al: Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non–small-cell lung cancer: A randomised, double-blind, phase 3 study. Lancet 374:1432-1440, 2009
11. Perol M, Chouaid C, Milleron, BJ, et al: Maintenance with either gemcitabine or erlotinib versus observation with predefined second-line treatmetn after cisplatin-gemcitabine induction chemotherapy in advanced NSCLC: IFCT-GFPC 0502 phase III study. J Clin Oncol 28, 2010 (suppl; abstr 7507)
12. Paz-Ares LG, De Marinis F, Dediu M, et al: PARAMOUNT: Phase III study of maintenance pemetrexed plus best supportive care versus placebo plus best supportive care immediatly following induction treatment with pemetrexed plus cisplatin for advanced nonsquamous non-small cell lung cancer. J Clin Oncol 29, 2011 (suppl; abstr CRA7510)
13. Cappuzzo F, Ciuleanu T, Stelmakh L, et al: Erlotinib as maintenance treatment in advanced non–small-cell lung cancer: A multicentre, randomised, placebo-controlled phase 3 study. Lancet Oncol 11:521-529, 2010
14. Therneau TM, Grambsch PM: Modeling Survival Data: Extending the Cox Model. New York, Springer, 2000.
15. Gundem G, Van Loo P, Kremeyer B, et al: The evolutionary history of lethal metastatic prostate cancer. Nature 520:353-357, 2015
16. Kim MY, Oskarsson T, Acharyya S, et al: Tumor self-seeding by circulating cancer cells. Cell 139:1315-1326, 2009
17. Twyman-Saint Victor C, Rech AJ, Maity A, et al: Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 520: 373-377, 2015

18. Sheu T, Heymach JV, Swisher SG, et al: Propensity score-matched analysis of comprehensive local therapy for oligometastatic non–small-cell lung cancer that did not progress after front-line chemotherapy. Int J Radiat Oncol Biol Phys 90:850-857, 2014
19. Petty WJ, Urbanic JJ, Ahmed T, et al: Long-term outcomes of a phase 2 trial of chemotherapy with consolidative radiation therapy for oligometastatic non–small-cell lung cancer. Int J Radiat Oncol Biol Phys 102:527-535, 2018
20. Xu Q, Zhou F, Liu H, et al: Consolidative local ablative therapy improves the survival of patients with synchronous oligometastatic NSCLC harboring *EGFR* activating mutation treated with first-line EGFR-TKIs. J Thorac Oncol 13:1383-1392, 2018

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Local Consolidative Therapy Vs. Maintenance Therapy or Observation for Patients With Oligometastatic Non–Small-Cell Lung Cancer: Long-Term Results of a Multi-Institutional, Phase II, Randomized Study

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/site/ifc.

Daniel R. Gomez
Honoraria: Varian Medical Systems, Merck, Bristol-Myers Squibb, AstraZeneca, Reflexion Medical, Vindico Medical Systems, US Oncology
Speakers' Bureau: Bristol-Myers Squibb, Varian Medical Systems
Research Funding: Merck, Varian Medical Systems, AstraZeneca, Bristol-Myers Squibb
Travel, Accommodations, Expenses: Varian Medical Systems, AstraZeneca, Merck, Vindico Medical Education, US Oncology, Driver

Jianjun Zhang
Honoraria: Roche, Sin-USA Biomedical Platform, Geneplus, Origimed, Innovent, CancerNet, Zhejiang Cancer Hospital
Consulting or Advisory Role: AstraZeneca, Geneplus, Beijing Institute, Capital Medical University
Research Funding: Merck

George R. Blumenschein Jr
Consulting or Advisory Role: Bristol-Myers Squibb, Bayer, Celgene, Clovis Oncology, AbbVie, ARIAD, Merck, Genentech, Novartis, Xcovery, Adicet, Amgen, AstraZeneca, Roche, MedImmune, Maverick Therapeutics
Research Funding: Merck, Celgene, Genentech, Xcovery, Novartis, Bayer Schering Pharma, Bristol-Myers Squibb, GlaxoSmithKline, Adaptimmune, Macrogenics, Kite Pharma, Immatics, Torque, Incyte, MedImmune, Exelixis, Immunocore, Roche, AstraZeneca

J. Jack Lee
Consulting or Advisory Role: AbbVie

Alexander V. Louie
Consulting or Advisory Role: AstraZeneca
Speakers' Bureau: Varian Medical Systems

D. Ross Camidge
Honoraria: Roche, G1 Therapeutics, Mersana, Takeda, AstraZeneca, Genoptix, Ignyta, Daiichi Sankyo, Hansoh, Lycera, Bio-Thera, Revolution Medicines
Research Funding: Takeda

Robert C. Doebele
Stock and Other Ownership Interests: Rain Therapeutics
Consulting or Advisory Role: OncoMed, Ignyta, GreenPeptide, AstraZeneca, Roche, Genentech, Bayer, Takeda, Rain Therapeutics
Research Funding: Ignyta (Inst)
Patents, Royalties, Other Intellectual Property: Licensing Fees from Abbott Molecular for Patent PCT/US2013/057495; Licensing fees from Ignyta for biologic materials (Inst); Licensing fees for biologic materials from Genentech (Inst); Licensing fees for patent from Rain Therapeutics
Travel, Accommodations, Expenses: Ignyta, Rain Therapeutics, Roche, Genentech

Ferdinandos Skoulidis
Honoraria: Bristol-Myers Squibb

Laurie E. Gaspar
Employment: BannerMDA Colorado
Honoraria: AstraZeneca
Consulting or Advisory Role: AstraZeneca
Other Relationship: American Assoc of Neurosurgery, National Cancer Institute Thoracic Malignancy Steering Committee

James W. Welsh
Employment: The University of Texas MD Anderson Cancer Center
Leadership: MolecularMatch
Stock and Other Ownership Interests: MolecularMatch
Honoraria: Shandong Cancer Hospital, Aileron Therapeutics, American Association of Physicists in Medicine, Nanobiotix, The Korean Society for Radiation Oncology
Consulting or Advisory Role: Reflexion Medical, MolecularMatch, Mavu Pharmaceutical, Oncorena, Checkmate Pharmaceuticals
Research Funding: Bristol-Myers Squibb, Merck, Aileron Therapeutics, Nanobiotix, Mavu Pharmaceutical, Checkmate Pharmaceuticals
Travel, Accommodations, Expenses: International Association for the Study of Lung Cancer, American Association for Cancer Research, Shandong Cancer Hospital, Turkish Society of Lung Cancer, Aileron Therapeutics, MedAustrion, Reflexion Medical, Gustave Roussy Cancer Center, Radiation Research Society, Nanobiotix, The Korean Society for Radiation Oncology, American Society for Radiation Oncology

Don L. Gibbons
Stock and Other Ownership Interests: Exact Sciences, Nektar
Consulting or Advisory Role: Sanofi, GlaxoSmithKline, Janssen Research & Development
Research Funding: Janssen Research & Development, Takeda, AstraZeneca
Travel, Accommodations, Expenses: AstraZeneca/MedImmune, BerGenBio, Takeda

Jose A. Karam
Honoraria: Pfizer, Roche, Genentech
Consulting or Advisory Role: Pfizer, Roche, Genentech
Research Funding: Roche (Inst), Genentech (Inst), Mirati Therapeutics (Inst)
Travel, Accommodations, Expenses: Pfizer, Roche, Genentech

Brian D. Kavanagh
Research Funding: Janssen (Inst)

Anne S. Tsao
Consulting or Advisory Role: Novartis, Boehringer Ingelheim, Genentech, Roche, MedImmune, Imedex, Lilly, Bristol-Myers Squibb, Epizyme, AstraZeneca, MedImmune, ARIAD, EMD Serono, Takeda, Heron
Research Funding: MedImmune (Inst), Merck (Inst), Genentech (Inst), Roche (Inst), Seattle Genetics, Millennium, Bristol-Myers Squibb (Inst), Boehringer Ingelheim (Inst), Polaris, Bristol-Myers Squibb
Patents, Royalties, Other Intellectual Property: UptoDate

Stephen G. Swisher
Travel, Accommodations, Expenses: Ethicon

John V. Heymach
Stock and Other Ownership Interests: Cardinal Spine, Bio-Tree
Consulting or Advisory Role: AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Spectrum Pharmaceuticals, Novartis, Genentech, Guardant Health, Hengrui Pharmaceutical, GlaxoSmithKline, EMD Serono, Merck, Lilly, Syntha Pharmaceutical
Research Funding: AstraZeneca (Inst), Spectrum Pharmaceuticals, Bayer, GlaxoSmithKline
Patents, Royalties, Other Intellectual Property: Licensing agreement between Spectrum and MD Anderson (including myself) regarding intellectual property for treatment of EGFR and HER2 exon 20 mutations

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Systemic and Local Therapy Regimens for All Patients From Random Assignment to Off Study

Patient	Sites of Disease at Random Assignment	Treatment Regimen From Random Assignment to Off Study
1	(1) Lung/lymph nodes	(1) 66 Gy in 33 fractions RT + paclitaxel (99 mg) + carboplatin (190 mg) IV per week
	(2) Spleen	(2) 50 Gy in four fractions
2	(1) Brain*	(1) Surgical resection
	(2) Lung/lymph nodes	(2) 60 Gy in 15 fractions RT to GTV, 52.5 Gy in 15 fractions to PTV with SIB
3	(1) Lung/lymph nodes	(1) 67.5 Gy in 27 fractions RT
	(2) Bone (humerus)	(2) 30 Gy in 10 fractions
4	(1) Lung/lymph nodes	(1) and (2) 70 Gy in 10 fractions (one field)
	(2) Pleura	Continued maintenance therapy: erlotinib 150 mg PO per day
5	(1) Brain*	(1) Surgical resection
	(2) Lung/lymph nodes	(2) Surgical resection
6	(1) Lung/lymph nodes	(1) 66 Gy in 30 fractions RT + paclitaxel (108 mg) + carboplatin (228 mg) IV per week
	(2) Metastatic lung	(2) 50 Gy in four fractions RT
7	(1) Lung	(1) and (2) treated to 50 Gy in four fractions
	(2) Metastatic lung lesions (n = 2)	
8	(1) Two brain lesions*	1) Gamma knife, 15 Gy and 20 Gy
	(2) Lung/lymph nodes	2) Not treated (experienced progression before local therapy)
9	(1) Two bony sites (T9 and left humerus)*	(1) 30 Gy in 10 fractions each
	(2) Lung/lymph nodes	(2) Surgical resection and PORT, 60 Gy in 30 fractions
10	(1) Lung	(1) 70 Gy in 10 fractions
	(2) Metastatic lung (n = 2 nodules)	(2) 50 Gy in 4 fractions
11	(1) Lung/lymph nodes	(1) Surgical resection and PORT, 45 Gy in 15 fractions
	(2) Metastatic lung	(2) Surgical resection
		Continued maintenance therapy: pemetrexed 500 mg/m^2
12	(1) Lung/lymph nodes	1) 52.5 Gy in 15 fractions to GTV, 45 Gy in 15 fractions to PTV with SIB
	(2) Bone No. 1 (right rib)	2) 45 Gy in 15 fractions
	3) Bone No. 2 (left iliac)	3) 40 Gy in 10 fractions
13	(1) Brain*	(1) Surgical resection + 15 Gy in one fraction to postoperative cavity
	(2) Bone (left iliac)	(2) 40 Gy in 10 fractions
14	(1) Two brain lesions*	(1) 20 Gy to both sites
	(2) Lung/lymph nodes	(2) 45 Gy in 15 fractions
15	(1) Lung/lymph nodes	(1) 52.5 Gy in 15 fractions to GTV, 45 Gy in 15 fractions to PTV with SIB
	(2) Adrenal	(2) Resection
	(3) Bone (L4)	(3) 18 Gy in one fraction

(continued on following page)

TABLE A1. Systemic and Local Therapy Regimens for All Patients From Random Assignment to Off Study (continued)

Patient	Sites of Disease at Random Assignment	Treatment Regimen From Random Assignment to Off Study
16	(1) Liver	(1) 50 Gy in 4 fractions
		Continued maintenance therapy: erlotinib 100 mg per day
17	(1) Bone (S1)	(1) 30 Gy in 10 fractions
	(2) Lung/lymph nodes	(2) 66 Gy in 30 fractions RT + pemetrexed (1,270 mg) + carboplatin (828 mg) IV per week
18	1) Brain	(1) No local treatment (disease responded to chemotherapy)
	2) Lung/Lymph Nodes	(2) 66 Gy in 30 fractions RT + paclitaxel (100 mg) + carboplatin (244 mg) IV per week
19	(1) Lung/lymph nodes	(1) 60 Gy in 30 fractions RT + pemetrexed (756 mg) + carboplatin (490 mg) IV per week
	(2) Bone (R iliac)	(2) Not treated (not visible after completion of chemoradiation)
20	(1) Lung/lymph nodes	(1) 52.5 Gy in 15 fractions
	(2) Liver	(2) 50 Gy in four fractions
21	(1) Lung/lymph nodes	(1) and (2) 45 Gy in 15 fractions
	(2) Cervical lymph nodes	
22	(1) Lung (primary site)	(1) 60 Gy in eight fractions
	(2) Adrenal	(2) 60 Gy in eight fractions
23	(1) Lung/lymph nodes	(1) and (2) 60 Gy in 30 fractions + cisplatin 25 mg/m^2 + etoposide 100 mg/m^2 IV every 21 days
	(2) Cervical lymph nodes	
24	(1) Lung (primary Site, pleural metastases resolved)	(1) 48 Gy in four fractions
		Continued maintenance therapy: crizotinib 250 mg PO twice per day
25	(1) Brain*	(1) 20 Gy in one fraction
	(2) Lung/lymph nodes	(2) 55 Gy in 15 fractions (350 in 10 fractions, then boost of 400 in five fractions)
		Continued maintenance therapy: erlotinib 100 mg PO per day
26	1) Lung/lymph nodes	Pemetrexed 500 mg/m^2 IV Q21 days
	(2) Spleen	
27	(1) Adrenal	Pemetrexed 840 mg every 21 days
28	(1) Lung/lymph nodes	Bevacizumab 1153 mg IV every 21 days
	(2) Adrenal	
29	(1) Lung/lymph nodes	Observation
	(2) Adrenal	
30	(1) Lung/lymph nodes	Pemetrexed 845 mg IV every 21 days
	(2) Bilateral adrenal glands	
31	(1) Brain*	Pemetrexed 612 mg IV every 21 days
	(2) Lung (primary site)	
32	(1) Brain*	Pemetrexed 1020 mg IV every 21 days
	(2) Lung/Lymph Nodes	
33	(1) Lung/Lymph Nodes	Pemetrexed 400 mg/m^2 IV every 21 days
	(2) Pleura	
34	(1) Brain*	Pemetrexed 860 mg IV every 21 days
	(2) Lung/lymph nodes	
35	(1) Lung/lymph nodes	Pemetrexed 400 mg/m^2 IV every 21 days
	(2) and (3) Two bony lesions (humerus and S1)	

(continued on following page)

TABLE A1. Systemic and Local Therapy Regimens for All Patients From Random Assignment to Off Study (continued)

Patient	Sites of Disease at Random Assignment	Treatment Regimen From Random Assignment to Off Study
36	(1) Lung/lymph nodes	Observation
	(2) Cervical lymph node	
37	(1) Lung/lymph nodes	Afatinib 40 mg PO per day
	(2) Adrenal gland	
38	(1) Lung/lymph nodes	Observation
	(2) Pleura	
39	(1) Lung (primary site)	Pemetrexed 905 mg IV every 21 days
	(2) Adrenal	
40	(1) Brain*	Pemetrexed 500 mg/m^2 IV every 21 days
	(2) Lung/Lymph Nodes	
41	1) Lung (primary site)	Erlotinib 100 mg PO per day
	(2) and (3) Two bones (T5 and L3)	
42	(1) Lung/lymph nodes	Observation
	(2) Pleura	
	(3) Metastatic lung lesion	
43	(1) and (2) Two brain lesions*	Pemetrexed 885 mg IV every 21 days
	(2) Lung/lymph nodes	
44	(1) Lung/lymph nodes	Pemetrexed 840 mg IV every 21 days
	(2) Bone (R ischium)	
45	(1) Lung/lymph nodes	Pemetrexed 825 mg IV every 21 days
	(2) Pleura	
46	(1) Lung/lymph nodes	Erlotinib 100 mg PO per day
	(2) and (3) Two pleural lesions	
47	(1) Lung/lymph nodes	Pemetrexed 500 mg/m^2 IV every 21 days
	(2) Paraspinal mass	
	(3) Cervical lymph node	
48	(1) Brain*	Pemetrexed 500 mg/m^2 IV every 21 days
	(2) and (3) Two lung lesions	
49	(1) Lung/lymph nodes	Pemetrexed 1,080 mg IV every 21 days
	(2) Right kidney	
	(3) Retroperitoneal lymph node	

NOTE. Off study reasons were progression or toxicity. Treatments were as follows: patients 1 through 25, local consolidated therapy arm; patients 26 through 49, maintenance therapy arm.

Abbreviations: GTV, gross tumor volume; IV, intravenously; PO, orally; PORT, postoperative radiation therapy; PTV, planning tumor volume; RT, radiation therapy; SIB, simultaneous integrated boost.

*Treated prior to random assignment.

TABLE A2. Salvage Therapies and Status of All Randomly Assigned Patients in the Study

Patient	Treatment Arm	Experienced Progression	Treatment Failed in New Lesion	Salvage Therapy	Complete LCT	Current Status
1	LCT	Yes	Yes	RT to bone lesion, systemic therapy clinical trial	No	AWD
2	LCT	No	NA	NA	NA	NCD
3	LCT	Yes	Yes	Nivolumab	No	AWD
4	LCT	No	NA	NA	NA	NED
5	LCT	Yes	Yes	Resection of progressive brain metastases	Yes	NED
6	LCT	Yes	Yes	Supportive care	No	DOD
7	LCT	No	NA	NA	NA	NED
8	LCT	Yes	Yes	Systemic Therapy on Clinical Trial	No	DOD
9	LCT	Yes	Yes	Palliative radiation therapy to bones, then erlotinib	No	DOD
10	LCT	Yes	Yes	RT to progressive bone lesion	Yes	NED
11	LCT	Yes	Yes	Clinical trial with RT + systemic therapy	No	DOD
12	LCT	Yes	Yes	Carboplatin + pemetrexed	No	DOD
13	LCT	No	NA	NA	NA	NED
14	LCT	Yes	Yes	Observation because of decreased performance status	No	DOD
15	LCT	Yes	Yes	RT to bulky sites of disease + afatinib	No	DOD
16	LCT	Yes	Yes	RT to sites of progressive disease + erlotinib	Yes	DOD
17	LCT	No	NA	NA	NA	NCD
18	LCT	Yes	No	RT + systemic therapy	Yes	AWD
19	LCT	Yes	Yes	Palliative WBRT + docetaxel	No	DOD
20	LCT	Yes	Yes	Systemic therapy clinical trial	No	AWD
21	LCT	Yes	Yes	Systemic therapy	No	AWD
22	LCT	NA	NA	NA	NA	NED
23	LCT	Yes	Yes	Craniotomy, postoperative WBRT, then systemic therapy	No	AWD
24	LCT	Yes	Yes	RT to progressive brain metastases	Yes	NED
25	LCT	Yes	Yes	RT to progressive sites of disease	Yes	AWD
26	MT/O	Early crossover	NA	NA	NA	NCD
27	MT/O	Yes	Yes	Adrenalectomy	Yes	DOD
28	MT/O	Yes	Yes	Palliative radiation to the mediastinum, then erlotinib	No	DOD
29	MT/O	Yes	Yes	Adrenalectomy	Yes	DOD
30	MT/O	Yes	Yes	Erlotinib	No	DOD
31	MT/O	Early crossover	NA	NA	NA	DOD
32	MT/O	Yes	Yes	RT to progressive sites of disease, then observation to remainder of disease	No	DOD
33	MT/O	Early crossover	NA	NA	NA	DOD
34	MT/O	Yes	No	Surgery to progressive lung lesion	Yes	NED
35	MT/O	Yes	Yes	Single-agent pemetrexed	No	DOD
36	MT/O	Yes	Yes	Palliative RT to mediastinum, then lost to follow-up	No	DOD

(continued on following page)

TABLE A2. Salvage Therapies and Status of All Randomly Assigned Patients in the Study (continued)

Patient	Treatment Arm	Experienced Progression	Treatment Failed in New Lesion	Salvage Therapy	Complete LCT	Current Status
37	MT/O	Yes	Yes	Chemotherapy + radiation/surgery to progressive sites of disease	Yes	DOD
38	MT/O	Yes	No	RT to progressive sites of disease	Yes	DOD
39	MT/O	Yes	Yes	RT to progressive sites of disease	Yes	DOD
40	MT/O	Yes	No	Supportive care (details lost to follow-up)	No	DOD
41	MT/O	Yes	No	Surgery to progressive site of disease	Yes	NED
42	MT/O	Yes	Yes	Clinical trial of systemic therapy followed by RT	Yes	NED
43	MT/O	Yes	Yes	Clinical trial with RT + systemic therapy	No	DOD
44	MT/O	Yes	Yes	Nivolumab	No	NED
45	MT/O	Yes	Yes	RT to progressive sites of disease	Yes	DOD
46	MT/O	No	NA	NA	NA	NED
47	MT/O	Yes	Yes	Observation, then nivolumab	No	AWD
48	MT/O	Yes	Yes	Supportive care	No	DOD
49	MT/O	Yes	Yes	Supportive care	No	DOD

Abbreviations: AWD, alive with disease; DOD, dead of disease; LCT, local consolidative therapy arm; MT/O, maintenance therapy/observation arm; NA, not available; NCD, noncancer death; NED, no evidence of disease; RT, radiation therapy; WBRT, whole-brain radiation therapy.