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Benchmarking Outcomes for Molecularly Characterized Synchronous Oligometastatic Non–Small-Cell Lung Cancer Reveals *EGFR* Mutations to Be Associated With Longer Overall Survival

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abstract

PURPOSE Local consolidative therapy (LCT) for patients with synchronous oligometastatic non–small-cell lung cancer is an evolving treatment strategy, but outcomes following LCT stratified by genetic mutations have not been reported. We sought to identify genomic associations with overall survival (OS) and progression-free survival (PFS) for these patients.

METHODS We identified all patients presenting between 2000 and 2017 with stage IV non–small-cell lung cancer and ≤ 3 synchronous metastatic sites. Patients were grouped according to mutational statuses. Primary outcomes included OS and PFS following initial diagnosis.

RESULTS Of 194 included patients, 121 received comprehensive LCT to all sites of disease with either surgery or radiation. *TP53* mutations were identified in 40 of 78 (55%), *KRAS* in 32 of 95 (34%), *EGFR* in 24 of 109 (22%), and *STK11* in nine of 77 (12%). At median follow-up of 96 months, median OS and PFS were 26 (95% CI, 23 to 31) months and 11 (95% CI, 9 to 13) months, respectively. On multivariable analysis, patients with *EGFR* mutations had lower mortality risk (hazard ratio [HR], 0.53; 95% CI, 0.29 to 0.98; $P = .044$) compared with wild-type patients, and patients with *STK11* mutations had higher risk of progression or mortality (HR, 2.32; 95% CI, 1.12 to 4.79; $P = .023$) compared with wild-type patients. *TP53* and *KRAS* mutations were not associated with OS or PFS. Among 71 patients with known *EGFR* mutational status who received comprehensive LCT, *EGFR* mutations were associated with lower mortality compared with wild-type (HR, 0.45; 95% CI, 0.22 to 0.94; $P = .032$).

CONCLUSION When compared with wild-type patients, those with *EGFR* and *STK11* mutations had longer OS and shorter PFS, respectively. *EGFR* mutations were associated with longer OS among oligometastatic patients treated with comprehensive LCT in addition to systemic therapy.

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ASSOCIATED CONTENT

Data Supplement

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

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INTRODUCTION

Roughly half of all patients with non–small-cell lung cancer (NSCLC) initially present with distant metastases, and 30% of these present with a limited number of metastases, a state often termed oligometastatic disease.[1] Although the definition of oligometastatic state continues to evolve, it generally refers to patients with one to five discrete metastatic lesions and is associated with a more favorable prognosis versus widely metastatic disease.[2,3] For these patients, several recent prospective studies demonstrated that comprehensive treatment with local consolidative therapy to all sites of disease (cLCT) led to significant improvements in both progression-free survival (PFS) and overall survival (OS) compared with treatment with systemic therapy alone.[4-7] Furthermore, several retrospective series have also shown that cLCT is associated with prolonged survival among patients presenting with synchronous oligometastatic NSCLC.[8-10]

Concurrently, there has been growing interest in the development of molecularly targeted agents that can be used in lieu of cytotoxic chemotherapy for patients with advanced disease. Current guidelines recommend testing for molecular biomarkers in NSCLC to guide therapy. Testing for actionable mutations/alterations of

CONTEXT

Key Objective

Local consolidative therapy (LCT) for patients with synchronous oligometastatic non–small-cell lung cancer is an evolving treatment strategy, but outcomes following LCT stratified by genetic mutations have not been reported. This retrospective cohort study aimed to identify genomic associations with outcomes for these patients.

Knowledge Generated

In this cohort study of 194 patients, we provide evidence that *EGFR* mutations are associated with longer overall survival (OS) and that *STK11* mutations are associated with shorter progression-free survival. We also demonstrate that patients with *EGFR* mutations who received both *EGFR*-targeted therapy and comprehensive LCT had significantly longer overall survival than those with *EGFR* wild-type tumors (98 *v* 29 months).

Relevance

These findings suggest that comprehensive LCT, when combined with molecularly targeted therapy for *EGFR*-mutated patients, may enable long-term survival. As novel molecularly targeted therapies emerge, treatment combining comprehensive LCT with targeted therapy in selected patients warrants further investigation.

EGFR, *ALK*, *ROS1*, *MET*, *BRAF*, and *NTRK* has been increasingly performed over the past two decades.[11-13] Tyrosine kinase inhibitors (TKIs) targeting these mutations and their downstream effectors have enabled long-term survival.[14,15] Despite the parallel efforts of investigation into cLCT and development of targeted therapies in stage IV disease, few studies have characterized the outcomes of patients with NSCLC receiving cLCT on the basis of genetic alterations.[16,17] Furthermore, such investigations have been limited to alterations of *EGFR* without broader consideration of other mutations, for which novel agents are likely to be approved in the coming years.[18,19] Therefore, we aimed to understand patterns of molecular alterations in patients presenting with synchronous oligometastatic NSCLC, and to identify associations with outcomes.

METHODS

Patient Selection

After approval by the University of Texas MD Anderson Cancer Center Institutional Review Board (PA16-0061), we identified patients presenting to our institution between January 1, 2000, and December 31, 2017, with stage IV NSCLC and ≤ 3 synchronous (defined as present at the time of initial diagnosis) metastatic lesions. Cohort selection has been previously described.[16] We used the MD Anderson Cancer Center GEMINI database, a prospectively collected database including tumor molecular profiles. Discrete metastatic foci within a single organ were counted as separate sites.[4] Intrathoracic nodal disease was counted as a single site, regardless of the number of nodes involved, consistent with categorizations previously described.[4] Intrathoracic disease stage was assigned using the American Joint Committee on Cancer 8th Edition staging system.[20] The radiographic response to initial systemic therapy was assessed using RECIST 1.1 criteria.[21] Patients who had local therapy to the primary and all metastatic lesions were considered to have received comprehensive LCT; patients receiving local therapy to some but not all of the sites were considered to have received subcomprehensive LCT; patients not treated with local therapy to any site were considered to have received no LCT. Radiotherapy (RT) treatment details have been previously reported.[22]

Molecular Profiling

Mutations were characterized for the majority of patients using next-generation sequencing (NGS) analysis using either solid tumor tissue or circulating cell-free DNA (cfDNA). Testing was performed most commonly with the Guardant360 CDx panel (Guardant Health, Palo Alto, CA) consisting of up to 129 genes and associated biomarkers, or with the FoundationOne CDx panel (Foundation Medicine, Cambridge, MA) consisting of up to 324 genes and associated biomarkers.[23,24] Additionally, immunohistochemistry and other testing was ordered at the discretion of the treating physician. Particularly for patients who presented before 2014, testing of single genes (eg, *EGFR*, *ALK*, and *KRAS*) was more commonly performed than panel testing.

Statistical Analysis

Fisher exact tests were used to assess the associations between categorical variables, and Wilcoxon rank-sum tests were used to assess associations between continuous variables between the treatment cohorts. The median follow-up time with associated CI was calculated using the reverse Kaplan-Meier method. Time-to-event end points considered latencies following initial diagnosis and were analyzed using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariable Cox analyses were used to determine associations with outcomes. The proportional hazards assumptions for all univariable and multivariable models were evaluated using chi-square tests of Schoenfeld residuals. Tests of the proportional hazards assumptions for death and progression or death using Schoenfeld residuals all yielded $P > .05$

and thus we failed to reject the null hypotheses that hazards were proportional. A *P* value threshold of ≤ .05 on univariate analysis was used to select variables for inclusion in each corresponding multivariable model. Statistical analysis was performed with Stata Version 16.1 (StataCorp, College Station, TX).

RESULTS

Baseline Characteristics

A total of 194 patients met inclusion criteria for this study. The patient, disease, and treatment characteristics are displayed in Table 1. A majority of patients were male (57%) and had Eastern Cooperative Oncology Group (ECOG) performance status of 0-1 (91%) at initial diagnosis. The median age at initial diagnosis was 62 years (range, 29-89 years). Most patients (77%) presented with adenocarcinoma histology. The most common sites of metastatic disease at diagnosis were brain (44%), bone (26%), and adrenal glands (19%). Most patients (71%) presented with at least two metastatic sites and most (92%) had disease confined to one discrete organ site.

First-line systemic therapy was administered to 90% of patients, with 72% receiving platinum-containing chemotherapy and 18% receiving TKIs with or without chemotherapy. The response to first-line therapy was partial or complete in 47%, stable disease or mixed response in 26%, and progression of disease in 15%; response was unable to be assessed in 12%, given no restaging imaging. LCT was given to the primary site in 145/194 (76%), with 114/145 (79%) of these patients receiving RT alone, 28/145 (19%) receiving surgery alone, and 2/145 (1%) receiving surgery followed by adjuvant RT. LCT was given to metastatic sites in 151/194 (78%) of patients, with 108/151 (72%) of these patients receiving RT alone, 35/151 (23%) receiving surgery alone, and 8/194 (5%) receiving surgery and RT. Comprehensive LCT was provided for 121/194 (62%) patients, subcomprehensive LCT for 52/194 (27%), and no LCT for 21/194 (11%).

Mutational Profiling and Use of Targeted Therapy

Of 194 patients in this series, 112 (58%) had available mutational data. Of these, 69% were tested using an NGS gene panel, whereas 31% were tested specifically for one or more individual genes. The most commonly mutated genes (Data Supplement) were *TP53* (43/78; 55%), *KRAS* (32/95; 34%), and *EGFR* (24/109; 22%). Of 24 patients with *EGFR* mutations, five (21%) had a T790M mutation. Only 28 patients in this series received PD-L1 testing; of these, 20 (71%) had a PD-L1 tumor proportion score > 1. The most common co-occurring mutations (Data Supplement) were in *TP53* and *KRAS* (n = 15), *TP53* and PD-L1 tumor proportion score > 1 (n = 14), and *TP53* and *EGFR* (n = 10). Among the 24 patients with *EGFR* mutations, 19 received an *EGFR*-targeted TKI at some point in their

Table 1. Baseline Patient, Disease, and Treatment Characteristics

Attribute	Value (n = 194)
Sex, No. (%)	
Female	83 (43)
Male	111 (57)
Median age at initial diagnosis, years (range)	62 (29-89)
Smoking status, No. (%)	
Current	66 (34)
Former (quit > 1 year before diagnosis)	95 (49)
Never	33 (17)
Median pack-year smoking history (IQR; n = 161)	40 (24-54)
ECOG performance status at diagnosis, No. (%)	
0	61 (31)
1	117 (60)
2	16 (8)
Histology, No. (%)	
Adenocarcinoma	149 (77)
Squamous	30 (15)
Other	15 (8)
Median primary tumor size, cm (range)	3.7 (1.0-12.0)
T stage, No. (%)	
1	44 (23)
2	73 (38)
3	51 (26)
4	26 (13)
N stage, No. (%)	
0	65 (34)
1	30 (15)
2	77 (40)
3	22 (11)
Sites of metastatic disease at diagnosis, No. (%)	
Brain	86 (44)
Bone	51 (26)
Adrenal	37 (19)
Contralateral lung	11 (6)
Liver	7 (4)
Nonregional nodes	6 (3)
No. of metastatic sites, (%)	
1	56 (29)
2	103 (53)
3	35 (18)
No. of discrete organ sites involved by metastases, (%)	
1	179 (92)
2	14 (7)
3	1 (1)

(Continued on following page)

Table 1. Baseline Patient, Disease, and Treatment Characteristics (Continued)

Attribute	Value (n = 194)
First-line systemic therapy, No. (%)	175 (90)
Platinum-containing agents	140 (72)
Targeted therapy	34 (18)
Response to first-line systemic therapy, No. (%)	
Response (partial or complete)	92 (47)
Stable disease/mixed response	50 (26)
Progression of disease	29 (15)
Unknown	4 (2)
LCT for primary, No. (%)	
No	47 (24)
Yes	147 (76)
Surgery alone	27 (14)
Radiotherapy alone	117 (60)
Both surgery and radiotherapy	3 (2)
Any LCT for metastases, No. (%)	
No	44 (23)
Yes	150 (77)
Surgery alone	35 (18)
Radiotherapy alone	108 (56)
Both surgery and radiotherapy	9 (5)
LCT for all metastases	141 (73)
LCT for primary and all metastases	121 (62)
Any progression after initial therapy, No. (%)	163 (84)
Local failure at treated primary site	55 (34)
Distant failure at treated metastatic site	36 (22)
Distant failure at untreated metastatic site	113 (69)
Involving new organ sites	74 (65)
Involving organ sites with known metastases	39 (35)
Salvage therapy after progression, No. (%)	147 (76)
Systemic therapy	92 (47)
Radiotherapy	90 (46)
Surgery	13 (7)
All disease cleared with salvage (n = 147)	45 (31)
Median follow-up, months (95% CI)	96 (81-106)

Abbreviations: AJCC, American Joint Commission on Cancer; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group; LCT, local consolidative therapy; N, node; T, tumor.

disease course, whereas five did not, and were treated with chemotherapy alone.

Disease Control and Survival

With an updated median follow-up time of 96 months (95% CI, 81 to 106), the median OS and PFS for this cohort were 26 (95% CI, 23 to 31) months and 11 (95% CI, 9 to 13) months, respectively (Data Supplement). Survival estimates are shown in Table 2, both among all patients and in the subset of patients receiving LCT to all sites of disease. Among all patients, 1- and 3-year OS were estimated to be 79% (95% CI, 73 to 84) and 39% (95% CI, 32 to 46), respectively; 1- and 3-year PFS were estimated to be 48% (95% CI, 41 to 55) and 25% (95% CI, 4 to 56), respectively; survival estimates are similar to those previously reported.[8] Concordant results were seen for patients receiving LCT. When stratified by response to initial therapy, patients who had progression of disease with upfront systemic therapy had shorter survival (Data Supplement) compared with patients with stable disease or any response.

Univariate analyses of factors associated with OS and PFS are shown in the Data Supplement. Factors associated with shorter OS on univariate analysis included male sex, ECOG 2 performance status, squamous histology, and higher T stage, whereas factors associated with longer OS included LCT for all metastases and *EGFR* mutation. Factors associated with shorter PFS on univariate analysis included male sex, ECOG 2 performance status, squamous histology, and *STK11* mutation, whereas the only factor associated with longer PFS was receipt of cLCT. Multivariable analyses of factors associated with OS and PFS are shown in Table 3. After adjustment for covariates, squamous histology (hazard ratio [HR], 3.40; 95% CI, 1.47 to 7.86; P = .004) was associated with shorter OS and *EGFR* mutation (HR, 0.53; 95% CI, 0.29 to 0.98; P = .044) was associated with longer OS. After adjustment for covariates, male sex (HR, 1.74; 95% CI, 1.04 to 2.91; P = .033), squamous histology (HR, 4.51; 95% CI, 1.64 to 12.41; P = .004), and *STK11* mutation (HR, 2.32; 95% CI, 1.12 to 4.79; P = .023) were associated with shorter PFS.

Consistent with our prior analysis,[8] patients who received LCT to all sites had longer survival than those who did not (Data Supplement), with median OS times of 29 (95% CI, 25 to 42) and 22 (95% CI, 15 to 29) months, respectively. Median 1- and 3-year OS times among patients receiving LCT were estimated to be 84% (95% CI, 76 to 90) and 42% (95% CI, 33 to 51), respectively. However, a positive prognostic association was not reproduced on multivariable analysis when considering *EGFR* mutational status. On subgroup analysis of 112 patients receiving comprehensive LCT, only *EGFR* mutation (HR, 0.45; 95% CI, 0.22 to 0.94; P = .032) was found to be associated with longer OS on multivariable analysis (Data Supplement).

PFS stratified by *STK11* mutational status is shown in Figure 1A. OS stratified by *EGFR* mutational status is shown in Figure 1B, and OS stratified by *EGFR* mutational status for the subset of patients receiving LCT to all sites of disease is shown in Figure 1C. Survival curves stratified by *EGFR* mutational status and receipt of EGFR-targeted therapy are shown in Figure 1D. Patients with *EGFR* mutations who received targeted therapy at any point in their disease course had significantly longer survival than those who had *EGFR* mutations but did not receive targeted therapy or

TABLE 2. Time-to-Event Outcomes of Patients Stratified by the Most Commonly Mutated Genes (top) and Among Patients Receiving Comprehensive LCT (bottom)

	At 1 year		At 3 years	
Mutated Gene	**OS**	**PFS**	**OS**	**PFS**
Outcomes, % (95% CI) for all patients				
TP53 (n = 43)	88 (74 to 95)	63 (47 to 75)	50 (34 to 64)	21 (10 to 34)
KRAS (n = 32)	88 (70 to 95)	66 (47 to 79)	44 (26 to 61)	25 (12 to 41)
EGFR (n = 24)	96 (74 to 99)	67 (44 to 82)	67 (44 to 82)	21 (8 to 39)
KIT (n = 13)	85 (51 to 96)	62 (31 to 82)	54 (25 to 76)	23 (6 to 47)
STK11 (n = 9)	77 (35 to 94)	33 (8 to 62)	51 (16 to 78)	0
MET (n = 9)	89 (43 to 98)	56 (20 to 80)	63 (24 to 87)	11 (1 to 39)
CDKN2A (n = 8)	87 (36 to 98)	50 (15 to 77)	72 (27 to 92)	25 (4 to 56)
All patients (n = 194)	79 (73 to 84)	48 (41 to 55)	39 (32 to 46)	17 (12 to 23)
Outcomes, % (95% CI) for patients receiving cLCT				
TP53 (n = 30)	87 (68 to 95)	63 (44 to 78)	40 (23 to 57)	20 (8 to 36)
KRAS (n = 23)	91 (69 to 98)	74 (51 to 87)	42 (21 to 61)	26 (11 to 45)
EGFR (n = 17)	100	71 (43 to 87)	65 (38 to 82)	18 (4 to 38)
KIT (n = 9)	89 (43 to 98)	67 (28 to 88)	44 (14 to 72)	22 (3 to 51)
STK11 (n = 5)	80 (20 to 97)	40 (5 to 75)	40 (5 to 75)	0
MET (n = 4)	75 (13 to 96)	50 (6 to 84)	75 (13 to 96)	25 (1 to 67)
CDKN2A (n = 5)	80 (20 to 97)	40 (5 to 75)	60 (13 to 88)	20 (1 to 58)
cLCT patients (n = 121)	84 (76 to 90)	56 (47 to 64)	42 (33 to 51)	21 (14 to 28)

Abbreviations: LCT, local consolidative therapy; OS, overall survival; PFS, progression-free survival.

those who did not have *EGFR* mutations. Estimates for 1- and 3-year OS by mutated gene are provided in Table 2. *EGFR*-mutated patients had 1- and 3-year OS of 96% (95% CI, 74 to 99) and 67% (95% CI, 44 to 82), respectively. *STK11*-mutated patients had 1- and 3-year PFS of 33% (95% 8 to 62) and 0%, respectively. Notably, patients with *EGFR* mutations who received TKIs had a median survival of 87 months (95% CI, 41 to undefined). Among the subset of these patients who also received LCT to all sites of disease, median survival was 98 months (95% CI, 31 to undefined). The presence of an *EGFR* T790M mutation was not associated with significantly different OS or PFS (Data Supplement). Patient-level outcomes for 112 molecularly characterized patients are provided in Figure 2.

After initial therapy, progression occurred in 84% of patients; the most common sites of first progression were distant, untreated sites (69%) and primary disease (34%), followed by distant sites treated by local therapy (22%), accounting for multiple sites of synchronous progression for some patients. Salvage therapy was used in 90% of patients who experienced failure; of these, 63% received systemic therapy, 61% received RT, and 9% received surgery.

DISCUSSION

In this study of 194 patients with synchronous oligometastatic NSCLC, we demonstrate with a median follow-up time of 8 years that cLCT is associated with favorable survival, with a median OS of 29 months with cLCT and 1- and 3-year survival rates of 84% and 42%, respectively. We characterized the mutational landscape of 112 of these 194 patients, showing that *TP53*, *KRAS*, *EGFR*, and *KIT* mutations were most commonly found on molecular testing. We provide initial benchmark data showing differential outcomes associated with mutation status, including potentially significant associations of *EGFR* mutation with longer OS and association of *STK11* (*LKB1*) mutations with significantly shorter PFS.

Several large-scale sequencing efforts characterizing the mutational landscape for metastatic NSCLC have been reported, but few efforts have focused on synchronous oligometastatic disease in particular. A recent study of polymetastatic disease identified enrichment of *ALK* mutations, *ALK* and *ROS1* fusions, and *MET* copy-number gains in metastatic sites compared with primary tumors.[25] Data show that driver alterations derived from NSCLC primary tumors may be shared across metastatic sites. However, metastatic clones may acquire new genetic alterations, highlighting the importance of adjuncts to systemic therapy to overcome genetic divergence, and consideration of repeat NGS testing, particularly if there is disease progression on a prior systemic agent.[26] In contrast to polymetastatic NSCLC, oligometastatic disease generally has fewer mutations and may have not yet realized its full metastatic potential, underscoring the importance of LCT to eradicate resistant clones.[27,28]

TABLE 3. Multivariable Cox Analysis of Factors Associated With OS and PFS Following Initial Diagnosis

	OS (n = 109)			PFS (n = 77)		
Attribute	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Male sex	1.30	0.8 to 2.06	.268	1.74	1.04 to 2.91	.033*
Age at diagnosis, years	—	—	—	—	—	—
Smoking status	—	—	—	—	—	—
Never	—	—	—	—	—	—
Former	—	—	—	—	—	—
Current	—	—	—	—	—	—
ECOG performance status						
0	Ref			Ref		
1	1.16	0.68 to 1.98	.589	1.31	0.77 to 2.23	.314
2	1.92	0.82 to 4.48	.131	2.32	0.85 to 6.37	.102
Histology						
Adenocarcinoma	Ref			Ref		
Squamous	3.40	1.47 to 7.86	.004*	4.51	1.64 to 12.41	.004*
Other	2.43	0.90 to 6.55	.079	0.49	0.06 to 3.78	.497
T stage						
1-2	Ref			—	—	—
3-4	1.28	0.79 to 2.07	.322	—	—	—
Brain metastases	—	—	—	—	—	—
Bone metastases	—	—	—	—	—	—
Adrenal metastases	—	—	—	—	—	—
No. of metastatic sites	—	—	—	—	—	—
1	—	—	—	—	—	—
> 1	—	—	—	—	—	—
No. of discrete organ sites involved by metastases						
1	—	—	—	—	—	—
> 1	—	—	—	—	—	—
LCT for all metastases	1.01	0.62 to 1.64	.983	0.81	0.49 to 1.33	.405
TP53 mutation (n = 43)	—	—	—	—	—	—
KRAS mutation (n = 32)	—	—	—	—	—	—
EGFR mutation (n = 24)	0.53	0.29 to 0.98	.044*	—	—	—
KIT mutation (n = 13)	—	—	—	—	—	—
STK11 mutation (n = 9)	—	—	—	2.32	1.12 to 4.79	.023*
MET mutation (n = 9)	—	—	—	—	—	—
CDKN2A mutation (n = 8)	—	—	—	—	—	—

NOTE. A *P* value threshold of ≤ .05 on univariate analysis was used to select variables for multivariable analysis. "—" indicates variables that did not meet criteria for inclusion in multivariable model.

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; LCT, local consolidative therapy; OS, overall survival; PFS, progression-free survival.

*Significant at $P < .05$.

The presence an *EGFR* mutation in a patient with stage IV oligometastatic NSCLC prompts several considerations regarding workup and management. Patients with *EGFR* mutations are more likely to develop brain metastases,[29] yet have longer survival. This is particularly true with receipt of TKI therapy combined with LCT to oligometastatic and oligoprogressive sites, irrespective of type of *EGFR* mutation or site of metastasis.[30,31] Several studies have suggested that comprehensive LCT should be considered for patients who do not show progression on systemic therapy. Our data similarly support that patients who experience progression on upfront systemic therapy may have shorter survival

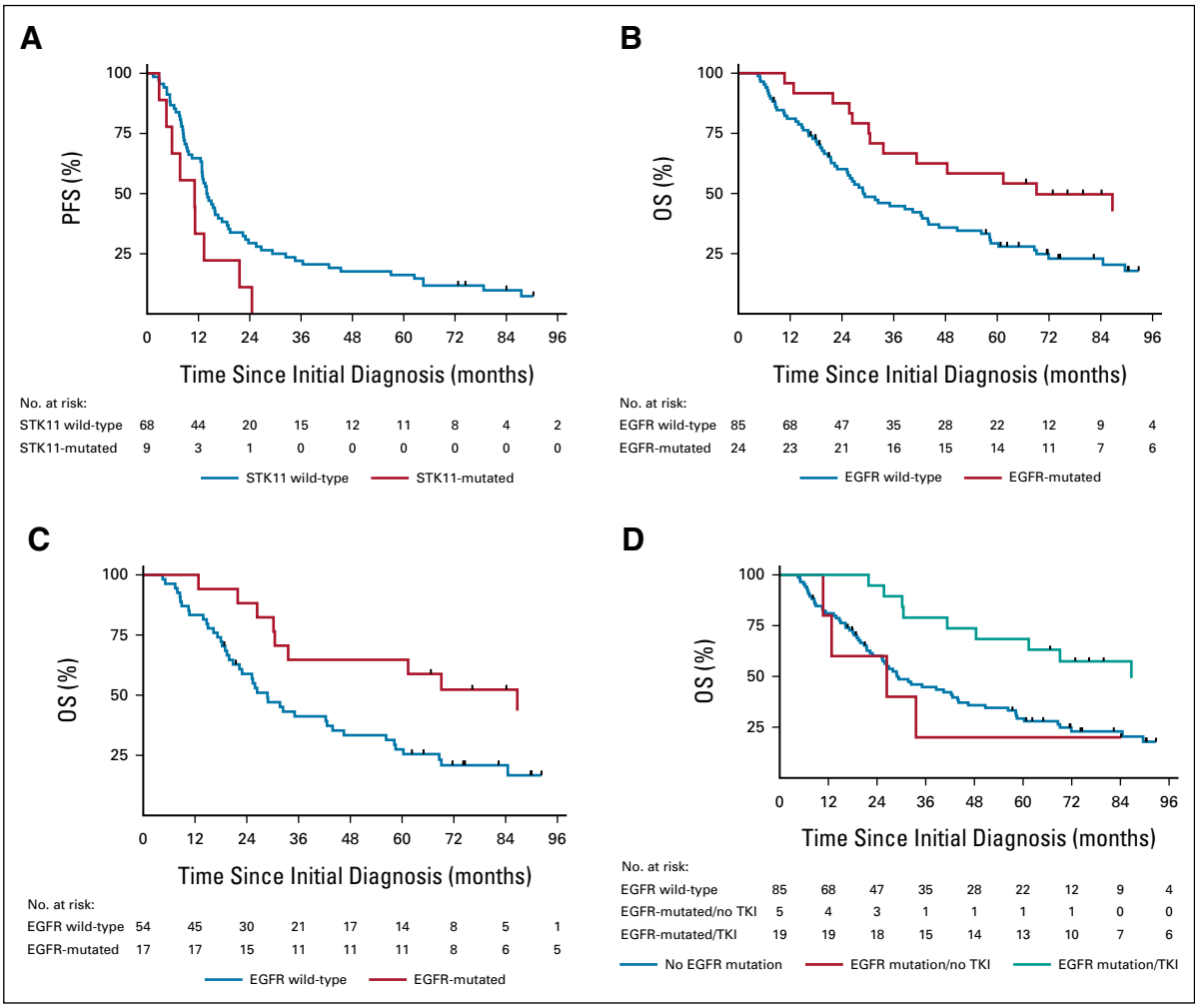

FIG 1. (A) PFS by *STK11* mutational status, (B) OS by *EGFR* mutational status, (C) OS by *EGFR* mutational status among patients receiving comprehensive LCT, and (D) OS of patients without *EGFR* mutations, with *EGFR* mutations without receipt of *EGFR*-targeted therapy, and with *EGFR* mutations with receipt of *EGFR*-targeted therapy. LCT, local consolidative therapy; OS, overall survival; PFS, progression-free survival; TKI, tyrosine kinase inhibitor.

despite use of LCT. Current guidelines also support the use of LCT after stable disease or partial response to first-line systemic therapy, although the ongoing phase III NRG LU002 (ClinicalTrials.gov identifier: NCT03137771), SARON (ClinicalTrials.gov identifier: NCT02417662), LONESTAR (ClinicalTrials.gov identifier: NCT03391869), and OMEGA (ClinicalTrials.gov identifier: NCT03827577) trials will further inform the effectiveness of this strategy.[32] There is growing evidence regarding the survival benefit associated with first-line TKI followed by LCT.[18,33] We previously reported that patients with *EGFR*-mutated metastatic NSCLC who received TKI followed by LCT had significantly longer PFS compared with treatment with TKI alone (36 *v* 14 months; $P = .0024$). Although our data suggest response to upfront systemic therapy as a potential predictor of benefit from LCT, the optimal use and timing of LCT in patients receiving systemic therapy remains an active area of investigation. An alternative strategy of using upfront RT to first-line TKI therapy for *EGFR*-mutated NSCLC showed an OS and PFS benefit in the recently published SINDAS (ClinicalTrials.gov identifier: NCT02893332) trial.[34]

Importantly, we find through this analysis that patients with *EGFR* mutations receiving both TKIs and comprehensive LCT had the most favorable outcomes, with a median survival of 98 months, which is longer than that observed for any other mutational subset, and remarkably high, considering these patients all presented with stage IV disease at diagnosis. Indeed, this estimate is significantly longer than OS reported in several randomized studies examining the role of LCT,[4,6] including that seen in the phase III SINDAS trial, which had a reported median OS of 26 months. Although the optimal timing and sequencing of systemic therapy relative to LCT remains uncertain, it appears that use of LCT and TKI in this subset of patients may confer remarkably long-term survival.

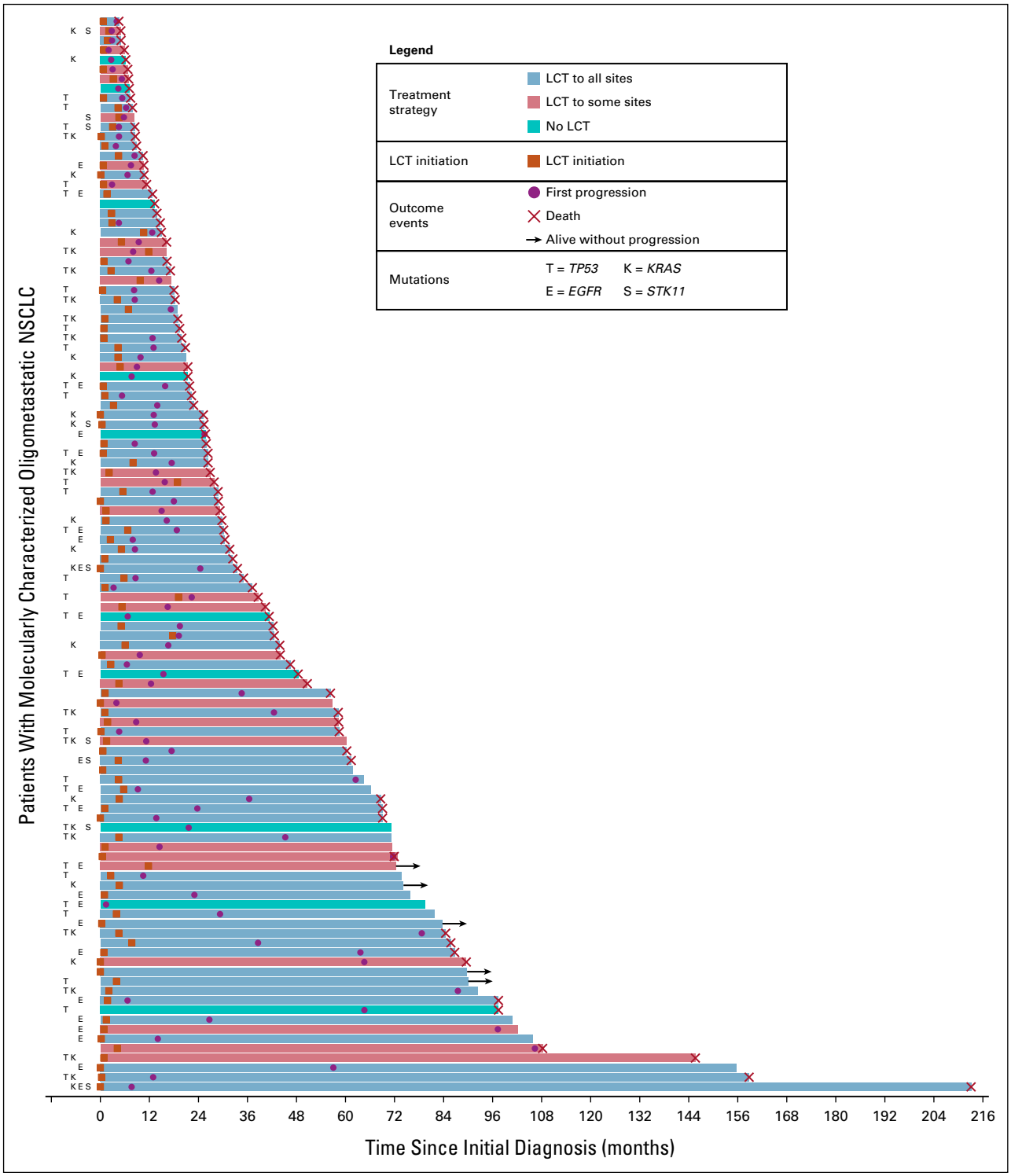

FIG 2. Patient-level outcomes for 112 patients with molecularly characterized oligometastatic NSCLC. The latency between diagnosis and outcome, either last follow-up or death, is represented by the length of each bar shown. Mutation statuses for common mutations are provided. LCT, local consolidative therapy, NSCLC, non–small-cell lung cancer.

We also found an association of *STK11* mutations with shorter PFS in this cohort. The negative prognostic value of *STK11* mutations, particularly in combination with *KRAS* mutations, has been previously reported in several series of polymetastatic NSCLC.[35,36] In the present series, the majority of patients with *STK11* (six of nine) mutations also had mutation in *KRAS*. *STK11/KRAS* comutation is hypothesized to limit responses to traditional systemic agents, along

with immunotherapy.[37-39] *KRAS* and *TP53* mutations did not correlate with either longer or shorter OS or PFS among patients with oligometastatic NSCLC, likely because of the lack of targeted therapies for these mutations. The United States Food and Drug Administration (FDA) approved sotorasib for patients with *KRAS* G12C-mutated NSCLC in 2021.[40] Investigators from the KRYSTAL study also recently reported favorable outcomes for adagrasib, including encouraging intracranial objective response rates; FDA-accelerated evaluation is pending.[41] APR-246, a small-molecule drug that binds to mutant p53 and restores its normal function, has been shown to induce apoptosis in NSCLC cell lines and may synergize with poly-[ADP-ribose] polymerase inhibitors to induce cell death.[42] As rationally designed therapies targeting molecular pathways emerge, survival differences between patients of with distinct mutational profiles may attenuate. We hypothesize that the benefit of cLCT may be more pronounced with these more effective systemic agents.

This study has several limitations. Although all patients had oligometastatic disease confirmed both radiographically and on biopsy, the sample is nevertheless heterogeneous with regard to sites of metastatic disease, use of LCT to primary and metastatic sites, and therapies preceding and following LCT. Probable selection bias exists for those patients able to tolerate and benefit most from *EGFR*-targeted therapies and comprehensive LCT. Molecular profiling in this study was nonuniform; although nearly 70% had comprehensive NGS panel testing, the remainder had testing of single genes, limiting our ability to make robust conclusions about less frequently seen mutations. The majority of patients in this study were treated before widespread use of checkpoint inhibitors, potentially limiting generalizability to patients treated in the present day. Perhaps, the most salient limitation is that it is not possible to understand the contribution of *EGFR*-targeted therapy versus LCT in prolonging survival; the results of prospective trials such as NORTHSTAR (ClinicalTrials.gov identifier: NCT03410043)[43] will be instrumental in better assessing the incremental benefit of LCT.

In conclusion, although the use of systemic therapies, including targeted agents, continues to evolve in the treatment of synchronous oligometastatic NSCLC, comprehensive LCT remains an important tool in selected patients. In this study, we stratified patients with synchronous oligometastatic NSCLC by genetic alterations to provide benchmarks for future comparison. Favorable outcomes were observed for patients with *EGFR* mutations, the majority of whom received *EGFR*-targeted agents. We also demonstrated that *STK11* mutations may be associated with shorter time to progression, highlighting the role of close surveillance following initial therapy. These data support ongoing trials to elucidate the utility and timing of LCT in patients with oligometastatic NSCLC receiving systemic agents. Further investigation into the prognostic and therapeutic implications of commonly seen mutations is warranted to optimize care for these patients.

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DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request within 1 year of publication.

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