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Significance of targeted therapy and genetic alterations in *EGFR*, *ALK*, or *KRAS* on survival in patients with non–small cell lung cancer treated with radiotherapy for brain metastases

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Background. We determined the impact of genetic alterations in *EGFR*, *ALK*, or *KRAS* on survival after radiotherapy for brain metastases in non–small cell lung cancer (NSCLC).

Methods. Of 172 genotyped NSCLC patients treated with radiotherapy for brain metastases in 2005–2012, 54 had cancers with *EGFR* mutations, 12 had *ALK* rearrangements, 38 had *KRAS* mutations, and 68 were wild-type (WT). Overall survival (OS) was determined.

Results. Median follow-up was 8.6 months. Median OS was 13.6 months for patients with *EGFR* mutations and 26.3 months for patients with *ALK* rearrangements, in contrast to 5.7 months for *KRAS*-mutant patients and 5.5 months for WT patients ($P = .001$). On multivariate analysis, adjusting for receipt of targeted therapy after cranial radiotherapy, *ALK* rearrangements were associated with improved OS (HR, 0.31; 95% CI, 0.13–0.74; $P = .008$). *EGFR* mutations were not significantly associated with improved OS on multivariate analysis (HR, 0.71; 95% CI, 0.37–1.38; $P = .3$). *KRAS* mutations were also not associated with improved OS (HR, 0.93; 95% CI, 0.59–1.47; $P = .8$). Receipt of targeted therapy after cranial radiotherapy was independently associated with improved OS (HR, 0.30; 95% CI, 0.17–0.54; $P < .001$). Receipt of chemotherapy after cranial radiotherapy, number of brain metastases, extracranial metastases, age, and performance status were also associated with OS.

Conclusions. NSCLC patients with genetic alterations in *ALK* have improved survival outcomes after radiotherapy for brain metastases compared with *EGFR, KRAS,* or WT. Subsequent receipt of targeted therapy was associated with additional improvement in OS.

Keywords: *ALK*, brain metastases, *EGFR*, non–small cell lung cancer, radiotherapy.

Non–small cell lung cancer (NSCLC) is increasingly defined by characteristic molecular changes in driver oncogenes. These include activating mutations in the epidermal growth factor receptor (*EGFR*)[1] and Kirsten rat sarcoma viral oncogene homolog (*KRAS*) genes[2] as well as rearrangements in anaplastic lymphoma kinase (*ALK*).[3] An analysis of 800 tumor samples by the Lung Cancer Mutation Consortium identified mutations in 54% of samples, with *KRAS* mutations (22%), *EGFR* mutations (17%), and *ALK* rearrangements (7%) being most common.[4]

The development of targeted therapy with tyrosine kinase inhibitors (TKIs) has led to improved outcomes for patients with *EGFR* mutations[5,6] or *ALK* rearrangements.[7] Treatment with EGFR TKIs (eg, erlotinib, gefitinib, and afatinib) in patients harboring *EGFR* mutations significantly improved progression-free survival (PFS) compared with chemotherapy.[8–11] Similarly, in a recent phase III trial, *ALK*-positive patients treated with the ALK TKI crizotinib in the second-line setting experienced improved PFS compared with standard chemotherapy.[12] Despite the impact of TKIs in patients with *EGFR* mutations and *ALK* rearrangements, there are currently no targeted therapy options for patients with *KRAS* mutations[13] or wild-type (WT) patients without a known driver mutation.

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Brain metastases are common in NSCLC, occurring in 20%–40% of patients,[14,15] and are associated with a poor median survival of 4–8 months.[16–18] The primary treatment for brain metastases is cranial radiotherapy, delivered using whole brain radiotherapy (WBRT), involved field radiotherapy (IFRT) to a smaller region of brain,[19] or stereotactic radiosurgery (SRS), with or without surgical resection.[20,21] Advancements in targeted therapy have led to the use of TKIs as initial therapy for selected patients with *EGFR* mutations or *ALK* rearrangements, typically with asymptomatic brain metastases and extracranial disease. However, radiotherapy remains the standard of care for the majority of NSCLC patients, including those with *EGFR* or *ALK* genetic alterations and symptomatic brain metastases, progressive brain metastases, or larger disease burden, and all patients without *EGFR* or *ALK* genetic alterations.[22,23] EGFR TKIs such as erlotinib are known to have some penetration of the blood-brain barrier.[24,25] Limited data on the ALK TKI crizotinib have suggested some central nervous system (CNS) activity,[26,27] and second-generation ALK TKIs with improved CNS penetration are under development.[28] Thus, the use of TKIs for patients with brain metastases and genetic alterations in *EGFR* or *ALK* is an area of ongoing investigation.

Currently, little is known about the relationship between NSCLC genetic subtype and prognosis after radiotherapy for brain metastases. The purpose of this study was to determine the significance of *EGFR*, *ALK*, and *KRAS* genetic alterations on outcomes after radiotherapy for brain metastases in NSCLC.

Materials and Methods

Case Identification

This retrospective study was approved by our Institutional Review Board. Patients with NSCLC were included if they were treated with radiotherapy for brain metastases at Massachusetts General Hospital (MGH) from 2005–2012 and had available tumor genotyping information. Our institution is a referral-based center with ample opportunities for mutation-specific clinical trials and novel treatments, thus attracting a unique distribution of patients, many of whom sought genotype testing.

Genotyping

Genotyping has been performed for NSCLC as part of routine care at MGH since 2004, at the clinical discretion of the treating physician. *EGFR* mutations were assessed by analyzing the *EGFR* kinase domain (exons 18–24) by polymerase chain reaction (PCR) and capillary gel electrophoresis. Since 2009, the allele-specific assay SNaPshot (Versions 1–3; Applied Biosystems) has also been used to detect >50 hot-spot mutation sites in 14 cancer genes.[29,30] *EGFR* mutations detected included G719-2155G, G719-2156G, T790-2369C, L858-2573T, L861-2582T, E746_A750-2235_2249del, and E746_A750-2236_2250del. In addition, a separate PCR was used to detect in-frame activating insertions or deletions in *EGFR* exons 19 and 20. *KRAS* mutations were detected by SNaPshot and included G12-34G, G12-35G, G13-37G, G13-38G, Q61-181C, Q61-182A, and Q61-183A. *ALK* rearrangements were identified by fluorescence in situ hybridization (Vysis LSI *ALK* [2p23] Dual Color, Break Apart Rearrangement Probe, Abbott Molecular). Samples were considered positive if more than 15% of cells showed split signals.[31] The majority of patients were genotyped at the time of initial diagnosis of NSCLC, typically from intrathoracic tissue such as the primary tumor or an involved lymph node. For a minority of those who had surgical resection of a brain metastasis (6% of all patients) and did not have prior genetic testing, genotyping was performed on the brain metastasis specimen.

Outcomes

Overall survival (OS) was assessed, calculated from the last day of the initial course of cranial radiotherapy. Electronic medical records and the Social Security Death Index were reviewed to determine the dates of patients' deaths.

Statistical Analysis

Fisher' exact tests were used for descriptive analyses. Survival curves were calculated using the Kaplan-Meier method and compared by log-rank tests. Multivariable analyses were conducted using Cox proportional hazards models, with selection of variables prior to analysis based on literature review and scientific principles. All *P* values were 2-tailed.

Results

Demographic, Clinical, and Brain Metastases Characteristics

Of 525 NSCLC patients treated with radiotherapy for brain metastases at our institution during the study period, 172 patients (33%) underwent genotyping that identified 54 with *EGFR* mutations (31%), 12 with *ALK* rearrangements (7%), 38 with *KRAS* mutations (22%), and 68 WT patients (40%). Median follow-up was 8.6 months for all patients (range, 0.2–131.3 months) and 9.5 months for surviving patients (range, 1.3–29.4 months). The median age was 60 years (range, 21–86 y). The 4 subgroups were not significantly different with respect to age, sex, race, or performance status (Table 1). There were higher rates of smokers in the *KRAS* and WT subgroups than in the *EGFR* and *ALK* subgroups ($P < .0001$). Patients initially presented with stage IV NSCLC in 74% of cases, and 56% had brain metastases at diagnosis. There was no significant association between genetic alteration status and presence of brain metastases at diagnosis of NSCLC or extent of extracranial disease at diagnosis of brain metastases. The 4 subgroups were not significantly different with respect to number, neuroanatomic location, or size of brain metastases.

Treatment Summary

The summary of treatments received by the study population is shown in Table 2. Thirty-three percent of *EGFR*-mutant patients and 17% of *ALK*-positive patients received TKI prior to the diagnosis of brain metastases, compared with 4% of WT and 0% of *KRAS*-mutant patients ($P = .2$). Only 2 *EGFR*-mutant patients (4%) received TKI as initial therapy for brain metastases prior to radiotherapy; both had been on TKI prior to diagnosis of

Table 1. Demographic, clinical, and brain metastases characteristics

Characteristic	All *n* (%)	*EGFR n* (%)	*ALK n* (%)	*KRAS n* (%)	WT *n* (%)	*P* value
Number of patients	172	54 (31)	12 (7)	38 (22)	68 (40)	–
Median age at diagnosis of BM (years)	60	58	58	59	66	.3
Sex						.2
Male	77 (45)	21 (39)	4 (33)	15 (39)	37 (54)	
Female	95 (55)	33 (61)	8 (67)	23 (61)	31 (46)	
Ethnic origin						.06
Asian	16 (9)	11 (20)	0 (0)	1 (3)	4 (6)	
Caucasian	143 (83)	38 (70)	12 (100)	34 (89)	59 (87)	
Other	13 (8)	5 (9)	0 (0)	3 (8)	5 (7)	
Smoking status						<.001
Never smoker	51 (30)	31 (57)	9 (75)	1 (3)	10 (15)	
Current/former	121 (70)	23 (43)	3 (25)	37 (97)	58 (85)	
ECOG performance status						.4
0–1	115 (67)	41 (76)	9 (75)	23 (61)	42 (62)	
2–4	57 (33)	13 (24)	3 (25)	15 (29)	26 (38)	
BM at diagnosis of NSCLC	97 (56)	31 (57)	7 (58)	20 (53)	39 (57)	.9
Extent of disease at diagnosis of BM						
Local control of primary tumor	55 (32)	14 (26)	4 (33)	16 (42)	21 (31)	.4
Extracranial metastases	122 (72)	44 (81)	9 (75)	22 (57)	47 (68)	.1
Number of BM						.6
1	66 (38)	15 (28)	5 (42)	16 (42)	30 (44)	
2–4	52 (30)	18 (33)	2 (17)	12 (32)	20 (29)	
≥5	54 (31)	21 (39)	5 (42)	10 (26)	18 (26)	
Neuroanatomic location if 1 BM ($n = 66$)	66	15	5	16	30	.3
Supratentorial	53 (88)	14 (93)	5 (100)	12 (75)	22 (73)	
Infratentorial	13 (12)	1 (7)	0 (0)	4 (25)	8 (27)	
Neuroanatomic location if ≥2 BM ($n = 106$)	106	39	7	22	38	.8
Supratentorial	29 (27)	11 (28)	2 (29)	7 (32)	9 (24)	
Infratentorial	6 (6)	3 (8)	0 (0)	1 (5)	2 (5)	
Both	71 (67)	25 (64)	5 (71)	14 (64)	27 (71)	
Size of largest BM (cm)						.3
Median (range)	1.5 (0.2–6.3)	1.2 (0.4–6.3)	1.4 (0.2–4.5)	2.0 (0.3–3.7)	1.8 (0.2–5.8)	

Abbreviations: BM, brain metastases; ECOG, Eastern Cooperative Oncology Group; NSCLC, non–small cell lung cancer.

Table 2. Treatment summary

	All *n* (%)	*EGFR n* (%)	*ALK n* (%)	*KRAS n* (%)	WT *n* (%)	*P* value
TKI before diagnosis of BM	23 (13)	18 (33)	2 (17)	0 (0)	3 (4)	.2
TKI as initial therapy for BM	2 (1)	2 (4)	0 (0)	0 (0)	0 (0)	–
Median time from diagnosis of BM to cranial radiotherapy (months)	0.9	0.9	0.8	1.0	1.0	.8
Initial cranial radiotherapy						
SRS/IFRT	47 (27)	16 (30)	5 (42)	10 (26)	16 (24)	.04
WBRT	124 (72)	38 (70)	7 (58)	28 (74)	51 (75)	.3
Surgical resection of BM	11 (6)	0 (0)	0 (0)	5 (13)	6 (9)	.02
Subsequent treatment following cranial radiotherapy						
Additional cranial radiotherapy	55 (32)	16 (30)	9 (75)	10 (26)	20 (29)	.02
EGFR TKI	62 (36)	45 (83)	0 (0)	2 (5)	15 (22)	< .001
ALK TKI	10 (6)	0 (0)	10 (83)	0 (0)	0 (0)	< .001
Chemotherapy	98 (57)	30 (56)	6 (50)	22 (58)	40 (59)	.9

Abbreviations: BM, brain metastases; IFRT, involved field radiotherapy; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor.

Table 3. Median overall survival in months

	EGFR	*ALK*	*KRAS*	WT	*P* value[a]
Median OS	13.6	26.3	5.7	5.5	.001

[a]For log-rank test.

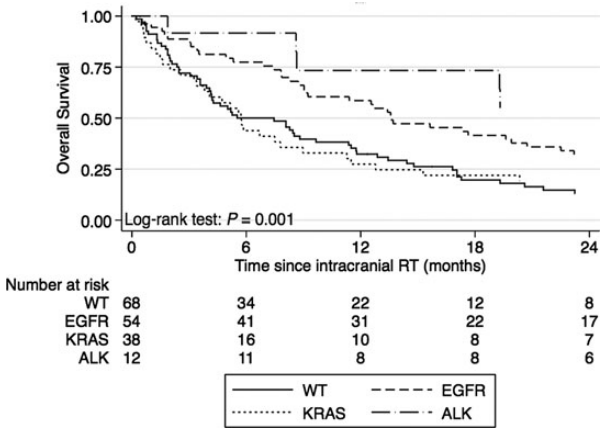

Fig. 1. Kaplan-Meier curves for overall survival.

brain metastasis. Comparing the 4 subgroups, there was no difference in time from diagnosis of brain metastases to intracranial radiotherapy (median, 0.9 months). The radiation technique was WBRT in 72% of patients to a median dose of 35 Gy; 27% received SRS/IFRT to a median dose of 18 Gy. Thirty percent of *EGFR*-mutant and 42% of *ALK*-positive patients received SRS/IFRT, in contrast to 24% of WT and 26% of *KRAS*-mutant patients ($P = .04$). After radiotherapy, 83% of *EGFR*-mutant patients received an EGFR TKI (84% of whom received erlotinib), compared with 22% of WT, 5% of *KRAS*-mutant, and 0% of *ALK*-positive patients ($P < .0001$). After radiotherapy, 83% of *ALK*-positive patients received an ALK TKI (90% of whom received crizotinib; 50% received a second generation TKI, ceritinib), compared with no patients in the other 3 subgroups ($P < .0001$).

Outcomes Following Cranial Radiotherapy

Median OS for the 4 subgroups is shown in Table 3, and the corresponding Kaplan-Meier curves are shown in Fig. 1. There was a highly significant difference in OS ($P = 0.001$) when comparing the 4 subgroups by log-rank test. Median OS was 13.6 months for *EGFR* and 26.3 months for *ALK*, in contrast to 5.7 months for *KRAS*, and 5.5 months for WT.

Multivariate Analysis

A multivariate Cox proportional hazards model was built using genetic alteration status, receipt of targeted therapy after cranial radiotherapy, receipt of chemotherapy after cranial irradiation, number of brain metastases, presence of extracranial metastases, age, and performance status (Table 4). *ALK* rearrangement status was significantly associated with improved OS (HR, 0.31; 95% CI, 0.13–0.74; $P = .008$). *EGFR* mutation status was not significantly associated with improved OS (HR, 0.71; 95% CI, 0.37–1.38; $P = .3$). *KRAS* mutation status was also not associated with differences in OS (HR, 0.93; 95% CI, 0.59–1.47; $P = .8$).

Table 4. Multivariate Cox proportional hazards model

Covariate	OS	
	HR (95% CI)	*P* value
EGFR	0.71 (0.37–1.38)	.3
ALK	**0.37 (0.15–0.92)**	**.03**
KRAS	0.93 (0.59–1.47)	.8
Targeted therapy	**0.32 (0.17–0.59)**	**<.001**
Chemotherapy	**0.39 (0.27–0.58)**	**<.001**
Number of brain metastases	**1.13 (1.04–1.25)**	**.007**
Extracranial metastases	**3.20 (2.02–5.07)**	**<.001**
Age	**1.02 (1.00–1.04)**	**.02**
ECOG Performance Status	**1.54 (1.07–2.23)**	**.02**

Abbreviations: HR, hazard ratio; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group.

Receipt of targeted therapy after cranial radiotherapy was strongly associated with improved OS (HR, 0.30; 95% CI, 0.17–0.54; $P < .001$), independent of genetic alteration status. Receipt of chemotherapy after radiotherapy was also strongly associated with improved OS. Number of brain metastases, presence of extracranial metastases, age, and decreased performance status were associated with worsened OS.

Impact of TKI Prior to Brain Metastasis Diagnosis

Patients with an *EGFR* mutation or *ALK* rearrangement on TKI prior to diagnosis of brain metastases (33% and 17%, respectively) had significantly worse outcomes than patients with these genetic alterations who were not on targeted therapy prior to brain metastasis diagnosis. Median OS was 9.0 versus 19.6 months ($P < .001$).

Discussion

The purpose of this study was to determine the impact of genetic alterations in *EGFR, ALK*, and *KRAS* on survival after radiotherapy for brain metastases in NSCLC. After adjustment for receipt of targeted therapy, receipt of chemotherapy, number of brain metastases, presence of extracranial metastases, age, and performance status, *ALK* rearrangements were associated with improved survival. Receipt of targeted therapy after cranial irradiation was also strongly associated with improved survival. Thus, the improved outcomes for patients with *ALK* genetic alterations in our study were likely due to both inherent tumor differences and the availability of targeted therapy. In contrast, with different tumor biology and no targeted therapy options, *KRAS*-mutant patients had similar outcomes to WT patients. *EGFR* mutations were significantly associated with improved OS on univariate analysis but were no longer

significant after adjustment for receipt of targeted therapy, perhaps reflecting the relative importance of targeted therapy for these patients. Data suggesting that *EGFR* mutations were associated with improved survival in NSCLC patients with brain metastases[32] may have predominantly reflected the benefit of targeted therapy. The number of *EGFR*-mutant patients in this study may also have been too small to detect a significant difference on multivariate analysis. There was no significant difference in time from brain metastasis diagnosis to receipt of cranial RT for patients with *EGFR* mutations compared with the other subgroups (median, 0.9 months, Table 2), and only 2 patients received EGFR TKIs prior to cranial RT, suggesting that there was no bias due to delay in RT or *EGFR*-mutant brain metastases being refractory to TKIs. However, it remains possible that there was confounding by the time of RT referral, with *EGFR*-mutant patients in our study having worse prognosis than in other series where patients did not receive cranial RT unless their brain metastases progressed on targeted therapy.

While other retrospective series have focused on local control and intracranial-relapse PFS in patients with brain metastases and *EGFR* or *ALK* genetic alterations,[33,34] our study focused on survival as the most clinically meaningful endpoint. Due to potential unreliability in the assessment of local control and death due to brain metastases in a retrospective setting, these endpoints were not evaluated in our study. Importantly, the distribution of patients in our study may not reflect the general population of patients with NSCLC due to our referral bias for those with specific genetic alterations including *EGFR* mutations and *ALK* rearrangements.

It is currently unclear whether *ALK* rearrangements are a prognostic biomarker, especially in the metastatic setting. A retrospective analysis of patients with advanced NSCLC, half of whom had brain metastases, reported no difference in survival comparing crizotinib-naïve *ALK*-positive patients with WT controls;[35] another study of stage IIIB/IV NSCLC in the pre-ALK inhibitor era also reported no difference.[36] However, a third study reported improved OS in NSCLC patients with malignant pleural effusions and *ALK* rearrangements who did not receive targeted therapy, compared with WT controls.[37] Our study is novel in that it addresses brain metastases specifically in an *ALK*-positive population that received targeted therapy.

In patients with early stage disease, as well as those with metastatic disease, *EGFR* mutations have been associated with improved survival, independent of treatment.[38,39] Of note, *EGFR* mutations occur more frequently in women, never-smokers, adenocarcinomas, and well-differentiated cancers, which may each portend a better prognosis.[40] *EGFR* and *KRAS* mutations were not associated with improved OS in a recent retrospective series of advanced NSCLC in the era of targeted therapies.[40] Some studies have demonstrated that *KRAS* is prognostic for poor outcomes in advanced NSCLC, although the control groups in these studies were heterogeneous[41,42] and specific *KRAS* mutations may be associated with different prognoses.[43] Both *ALK* and *EGFR* are clearly predictive biomarkers, as supported in this study, where receipt of ALK TKIs or EGFR TKIs was independently associated with improved survival. *KRAS* is a predictive biomarker for absence of response to EGFR TKIs.[44]

With respect to specific sites of metastases, Doebele et al found in treatment-naïve patients with stage IV NSCLC that *ALK* rearrangements were associated with pericardial, pleural, and liver metastases, *EGFR* mutations were associated with liver metastases, and *KRAS* mutations were not associated with any sites compared with WT controls.[45] No genetic alteration was associated with predisposition for brain, bone, adrenal, or lung metastases. Both *EGFR* and *KRAS* were not associated with incidence of brain or bone metastases in another series,[46] whereas *EGFR* was associated with more lesions in the brain and bone compared with WT controls in a third report.[47] In our study, we report the novel finding that genetic alterations in *ALK, EGFR,* and *KRAS* were not associated with significant differences in number, neuroanatomic distribution, or size of brain metastases among patients receiving cranial radiotherapy.

Targeted therapy may be used before the diagnosis of brain metastases, after diagnosis as initial therapy, and/or after diagnosis and cranial radiotherapy. Thirty-three percent of *EGFR*-mutant and 17% of *ALK*-positive patients received a TKI prior to diagnosis of brain metastases in our study. These patients had significantly worse outcomes compared with *EGFR*-mutant and *ALK*-positive patients not on TKIs prior to diagnosis of brain metastases, which was likely due to selection for resistant or more aggressive disease. The introduction of crizotinib occurred during our study period; one of the 2 *ALK*-positive patients who did not receive TKI before cranial radiotherapy was diagnosed with brain metastases before crizotinib was available through clinical trials at our institution or commercially. Only 2 *EGFR*-mutant patients received TKIs as initial therapy for brain metastases, which could reflect the relatively large size of the brain metastases in the study population (median, 1.5 cm overall; 1.2 cm for *EGFR*-mutant patients) as well as variations in treatment patterns during the study period. After radiotherapy, 83% of *EGFR*-mutant and *ALK*-positive patients received TKI. The strong effect of targeted therapy on improved survival after cranial radiotherapy was likely driven by the CNS activity of EGFR TKIs and the second-generation ALK TKI ceritinib on tumor cells still sensitive to these agents.

Strengths of our study include our comparison of 4 genetic subtypes of NSCLC and our multivariate model that adjusted for use of targeted therapy. Our study was inclusive of patients who received any cranial radiotherapy (with localized SRS/IFRT vs WBRT), reflecting common clinical practice. The major limitations of our study were its retrospective nature and the small sample size of some subgroups, with potential underpowering of some analyses. Pairwise comparisons were not performed in order to minimize over-analysis and multiple testing. In building the Cox proportional hazards model, we included traditional prognostic factors for survival including variables identified in the brain metastases graded prognostic assessment.[48] The receipt of any targeted therapy after cranial RT was included as a binary variable in the model, instead of introducing the complexity associated with receipt of multiple TKIs at variable time points for some patients. As more patients are identified by genetic alterations and more TKIs with variable CNS activity are introduced, this model can be refined. A future question that can also be answered when larger sample sizes are available is whether specific *ALK* rearrangements or *EGFR* mutations portend different prognoses.

In conclusion, *ALK* rearrangements are independently associated with improved survival outcomes in NSCLC patients who

receive radiotherapy for brain metastases compared with mutations in *EGFR* or *KRAS* or a WT genetic profile. Targeted therapy against *ALK* or *EGFR* after cranial radiotherapy is associated with additional survival benefit. The results of this study are encouraging for patients with brain metastases and genetic alterations in *ALK* or *EGFR*, who have targeted therapy options. As additional genetic subtypes of NSCLC are identified and targeted agents with improved blood-brain barrier penetration become available, the choreography of targeted therapy and radiotherapy will continue to evolve and likely translate into improved outcomes for more patients. The ability to apply what has been learned from the subset of patients with *ALK* or *EGFR* genetic alterations will be essential to improving outcomes in other molecularly defined subsets of NSCLC. Future prospective trials may focus on determining the optimal timing of cranial radiotherapy relative to targeted agents with activity against brain metastases, as well as the concurrent use of radiotherapy and targeted agents.

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Conflicts of interest statement. Dr. Gainor is a consultant for Boehringer-Ingelheim. Dr. Sequist is an uncompensated consultant for Clovis, Boehringer-Ingelheim, AstraZeneca, and Merrimack Pharmaceuticals. Dr. Shaw is a consultant for Pfizer, Novartis, Ariad, Chugai, and Daiichi-sankyo. Dr. Shih is a consultant for Novartis. All remaining authors have declared no conflicts of interest.

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