

# Management of Brain Metastases in Non–Small-Cell Lung Cancer

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Lung cancer is the leading cause of cancer-related death in the United States. Approximately 20% of these patients present with brain metastases (BMs). Surgical resection, stereotactic radiosurgery, and whole-brain radiation therapy have historically been the primary treatment modalities for patients with non–small-cell lung cancer (NSCLC) and BMs. The treatments for BMs have become complex with the discovery of targetable molecular drivers and the development of an astonishing number of tyrosine kinase inhibitors. Many of these tyrosine kinase inhibitors have robust and durable efficacy against CNS metastases. In many circumstances, these drugs can defer local therapy and even reduce the risk of CNS progression. More recently, immune checkpoint inhibitors have changed the treatment landscape for many patients with NSCLC; however, the role of immunotherapy in patients with BMs is the subject of ongoing investigations. This article will review the current data and our approach to patients with NSCLC and BMs.

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## INTRODUCTION

Lung cancer remains the leading cause of cancer-related mortality in the United States. Unfortunately, approximately 57% of patients with non–small-cell lung cancer (NSCLC) present with metastatic disease, and 20% present with brain metastases (BMs) at the time of diagnosis.<sup>1,2</sup> During the course of the disease, approximately 25% to 50% of patients will develop BMs.<sup>3</sup>

Historically, the brain was regarded as a sanctuary site for metastatic NSCLC because of the physical, chemical, and metabolic properties of the blood-brain barrier on preventing delivery of drugs to the CNS. Surgical resection, stereotactic radiosurgery (SRS), and whole-brain radiation therapy (WBRT) have been the primary treatment modalities. Insight into the biology of this disease has led to the development of an arsenal of novel treatments, including targeted agents and immune checkpoint inhibitors. The treatments for BMs have become more convoluted, especially in those patients with molecular drivers such as epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and, c-ros oncogene 1 (*ROS1*). Here, we review the management of patients with NSCLC and BMs and focus on the role of systemic therapy, especially chemotherapy, tyrosine kinase inhibitors (TKIs), and immunotherapy.

## LOCAL THERAPY IN THE MANAGEMENT OF BMs

There is significant heterogeneity in patients with BMs from NSCLC. Frequently, the selection of

local treatment is based on the number of BMs, size or location of BMs, symptoms of CNS and extra-CNS disease, presence or absence of actionable mutation, and patient and physician preferences. For patients with symptomatic or a limited number of BMs (often defined as 1 to 3), local therapy with neurosurgical resection or with SRS is considered.

Neurosurgical resection is often the standard of care for solitary or symptomatic BMs since resection will rapidly reduce symptoms. The combination of neurosurgical resection and postoperative radiation therapy was first investigated in patients who underwent resection of solitary BMs, and the results favored the combination treatment.<sup>4,5</sup> Subsequently, SRS was investigated in the postoperative setting. A phase III trial compared SRS to the resection cavity to observation in patients who underwent complete resection of 1 to 3 BMs (Table 1). This trial revealed a lower rate of local recurrence at 12 months in the SRS arm and similar overall survival (OS).<sup>6</sup> A phase III trial compared postoperative SRS to the surgical cavity with WBRT in patients who underwent resection of one BM and revealed a longer cognitive-free deterioration survival and shorter time to intracranial disease progression in patients assigned to SRS. OS was similar in the two arms.<sup>7</sup> These trials contributed to the adoption of SRS to the surgical resection bed as the preferred therapy.

### ASSOCIATED CONTENT

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**TABLE 1.** Select Phase III Trials of SRS in Patients With BMs

First Author	No. of Metastases and Treatment	Comparison of Treatment Types	No. of Patients	CNS Disease Control			OS		
				%	HR	P	Duration (months)*	HR	P
Mahajan <sup>6</sup>					0.46	.015		1.29	.24
	Complete resection of 1-3 BMs	Observation	68	43†			18		
		SRS	64	72			17		
Brown <sup>7</sup>					2.45	< .001		1.07	.70
	1 resected BM	SRS	98	—‡			12.2		
		WBRT	96	—‡			11.6		
Brown <sup>8</sup>						< .001		1.02	.92
	1-3 BMs treated with SRS	SRS	111	50.2§			10.4		
		SRS + WBRT	102	84.6			7.4		
Aoyama <sup>9</sup>						< .001			.42
	1-4 BMs treated with SRS	SRS	67	76.4			8.0		
		SRS + WBRT	65	46.8			7.5		
Kocher <sup>10</sup>						< .001		0.98	.89
	1-3 BMs treated with surgical resection or SRS	SRS or surgery alone	179	78¶			10.9		
		SRS or surgery + WBRT	180	48			10.7		
Mulvenna <sup>12</sup>								1.06	.80
	BM's unsuitable for SRS or surgical resection	WBRT + OSC	269	NA			9.2 weeks		
		OSC	269				8.5 weeks		

Abbreviations: BM, brain metastasis; HR, hazard ratio; NA, not available; OS, overall survival; OSC, optimal supportive care; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

\*Unless otherwise noted.

†Defined as 12-month freedom from local recurrence.

‡Defined as time to intracranial tumor progression. Intracranial disease control at 12 months was 36.6% for SRS and 72.1% for WBRT ( $P < .001$ ). Median time to intracranial disease progression for SRS and WBRT was 6.4 and 27.5 months, respectively.

§Local control and distant brain disease control at 12 months.

||A 12-month brain tumor recurrence rate.

¶Intracranial disease progression rate.

SRS is the logical treatment choice for patients who cannot undergo resection and/or have a limited number of BMs. However, there was a concern that the development of CNS disease outside the treatment area would compromise quality of life (QoL) and/or OS. Several phase III trials have investigated SRS alone compared with WBRT to address this clinical question (Table 1). A phase III trial enrolled patients with 1 to 3 BMs and randomly assigned patients to SRS alone or with WBRT.<sup>8</sup> Patients assigned to SRS alone compared with WBRT experienced less cognitive deterioration and a better QoL at 3 months, but shorter time to intracranial disease progression. A similar phase III trial investigated patients with 1 to 4 BMs and randomly assigned patients to SRS alone or with WBRT.<sup>9</sup> OS was similar in the two treatment arms, and the 12-month brain tumor recurrence rate and the need for salvage radiotherapy was higher in the SRS-alone arm. The European Organization for Research and Treatment of Cancer

performed a phase III trial of patients who underwent surgical resection or SRS (1 to 3 metastases) and randomly assigned patients to WBRT or observation.<sup>10</sup> The median time to deterioration of performance status and OS were similar in both arms, but patients assigned to the observation arm reported a better health-related QoL.<sup>11</sup>

These phase III trials enrolled patients with multiple tumor types and have revealed several consistent trends. Treatment with SRS is associated with a similar OS and better neurocognitive and/or QoL outcomes. The rate of intracranial relapse and need for salvage therapies is higher with SRS, so diligent surveillance is required for CNS progression. A common surveillance is magnetic resonance imaging scans of the brain once every 3 months. The role of WBRT is declining because of the increased concerns about the potential long-term neurocognitive effects, and a phase III trial revealed limited clinical benefit compared with best supportive care.<sup>12,13</sup>

## CHEMOTHERAPY AND IMMUNOTHERAPY IN PATIENTS WITH BMs

Historically, chemotherapy-based treatments were not used to treat BMs because of the low systemic response rate (RR) and the belief that the blood-brain barrier reduced penetration of chemotherapy agents and compromised efficacy. However, for patients with macroscopic metastases, there is often disruption of the blood-brain barrier and neovascularization, which allows exposure of the BM to therapeutic agents. Currently, most patients receive an immunotherapy-based treatment as first-line therapy.

Single-agent pembrolizumab is a standard first-line therapy for patients with programmed death-ligand 1 (PD-L1) expression, and in combination with platinum-based chemotherapy irrespective of PD-L1 expression.<sup>14-16</sup> Patients with untreated BMs were excluded from the previous trials of single-agent pembrolizumab.<sup>14,17</sup> A phase II trial investigated the efficacy of pembrolizumab in patients with BMs, and the observed RR was 33%.<sup>18</sup> In the phase III trials, patients with asymptomatic BMs (defined as the absence of neurologic symptoms, no requirement for corticosteroids, and no lesion > 1.5 cm) were eligible. The benefit observed in patients with BMs was similar to the intent-to-treat patient population, but the CNS RR of the subset of patients with untreated BMs is not known at this time.

## EGFR-MUTATED NSCLC

Approximately 10% to 15% of whites and 50% of Asians with NSCLC adenocarcinoma have an *EGFR*-activating mutation (*EGFR*-positive). BMs constitute a major problem for patients with *EGFR*-positive disease. The incidence of CNS metastases at diagnosis is approximately 24%, and it almost doubles at 3 years, despite treatment with a first- or second-generation TKI.<sup>19</sup> The CNS penetration of these agents is relatively low, and the brain is a pharmacokinetic sanctuary. Recently, osimertinib became the preferred

first-line TKI because of its tolerability, prolonged progression-free survival (PFS), and CNS efficacy compared with first-generation TKIs. We have summarized the activity of osimertinib in patients with *EGFR*-positive NSCLC and BMs in the following sections.

## Osimertinib

Osimertinib is a third-generation irreversible *EGFR* TKI that inhibits *EGFR*-sensitizing and T790M mutations (T790M-positive). Preclinical studies have shown osimertinib demonstrated better CNS penetration than erlotinib or gefitinib.<sup>20</sup> It was first approved in the second-line setting in patients that developed a T790M mutation after failure of a first-generation TKI.<sup>21</sup> A subgroup analysis demonstrated CNS RRs of 70% and 31% in patients with measurable disease treated with osimertinib and chemotherapy, respectively. The median intracranial PFS times were 11.7 months and 5.6 months, respectively.<sup>22</sup> A pooled analysis of 50 patients from two phase II studies of patients with T790M-positive disease and BMs revealed a CNS RR of 54% and a CNS disease control rate of 92%.<sup>23</sup>

Subsequently, osimertinib was approved in the first-line setting on the basis of the FLAURA (ClinicalTrials.gov identifier: [NCT02296125](https://clinicaltrials.gov/ct2/show/study/NCT02296125)) trial.<sup>24</sup> This trial provided the best data on the CNS efficacy of osimertinib compared with first-generation *EGFR* TKI. Patients were defined as CNS evaluable for response as having one or more measurable lesion. The CNS RRs in the osimertinib and first-generation TKI arms were 91% and 68%, respectively; disease control rates were 95% and 89%, respectively (Table 2). On a competing risk analysis, the estimated probability of observing a CNS progression event (in the absence of non-CNS progression event or death) at 12 months was 8% with osimertinib and 24% with erlotinib or gefitinib.<sup>25</sup>

Leptomeningeal metastases historically have been associated with a poor prognosis. The BLOOM (ClinicalTrials.gov identifier: [NCT02228369](https://clinicaltrials.gov/ct2/show/study/NCT02228369)) study was a phase II trial that evaluated osimertinib 160 mg in patients with *EGFR*-positive NSCLC and leptomeningeal metastases who had progressed on previous *EGFR* TKI. The overall leptomeningeal metastases response was 43% by investigator assessment. The most common adverse effects were grade 1 and 2 diarrhea, nausea, paronychia, and rash.<sup>26</sup> Osimertinib 160 mg once per day is well tolerated and is an option for patients with *EGFR*-positive disease and leptomeningeal metastases.

In summary, in patients with newly diagnosed *EGFR*-positive disease and symptomatic BMs, we recommend local therapy (SRS, surgery) followed by osimertinib. For those with asymptomatic BMs, we recommend osimertinib as first-line therapy (Fig 1A). In patients with symptomatic BMs that progressed during or after a first- or second-generation TKI, we recommend local therapy for symptomatic CNS disease followed by systemic therapy (osimertinib if T790M-positive; chemotherapy if T790M-negative). For those with asymptomatic BMs, we recommend osimertinib

**TABLE 2.** Efficacy of Osimertinib and First-Generation *EGFR* TKIs in Patients With BMs<sup>25</sup>

Efficacy Parameter	cFAS (%)		cEFR (%)	
	Osimertinib (n = 61)	Erlotinib or gefitinib (n = 67)	Osimertinib (n = 22)	Erlotinib or gefitinib (n = 19)
CNS ORR	66	43	91	68
CNS DCR	90	84	95	89
Median CNS DOR	NR	14.4	15.2	18.7

Abbreviations: BM, brain metastasis; cEFR, CNS evaluable for response; cFAS, CNS full analysis set; DCR, disease control rate; DOR, duration of response; *EGFR*, epidermal growth factor receptor; ORR, objective response rate; NR, not reached; TKI, tyrosine kinase inhibitor.

for those with *T790M*-positive disease followed by close surveillance or local therapy followed by chemotherapy for those with *T790M*-negative disease (Fig 1B).

### ALK-REARRANGED NSCLC

The *EML4-ALK* translocations (*ALK*-positive) are observed in approximately 5% of patients. BMs constitute a challenging problem for patients with *ALK*-positive disease as well. Approximately 30% to 40% of these patients have BMs at diagnosis.<sup>27-29</sup> In the crizotinib resistance setting, up to 70% of the patients have CNS disease.<sup>30</sup> Furthermore, the cumulative risk of developing CNS disease can reach 70% at 5 years after diagnosis, making the CNS the most common site of disease progression.<sup>31</sup> We discuss the data regarding *ALK* TKIs in patients with BMs in the following sections.

#### First-Generation TKI

**Crizotinib.** Crizotinib has activity against *ALK*, *MET*, and *ROS1*. It was the first TKI approved by the US Food and Drug Administration (FDA) in patients with *ALK*-positive disease on the basis of the PROFILE 1014 (ClinicalTrials.gov identifier: [NCT01154140](#)) trial. However, the low CNS penetration of crizotinib was a significant therapeutic weakness, especially for patients with baseline BMs. A retrospective analysis of crizotinib in patients with BMs from the PROFILE 1005 and PROFILE 1007 trials revealed an intracranial response rate of 18% among those with untreated BMs and 33% among those with treated BMs. The median intracranial PFS was 5.9 months and 6 months among those with untreated and treated BMs, respectively. For patients with previously untreated and treated BMs, the CNS was the most common site of progression in approximately 70% of the patients.<sup>27</sup> These data and data from other trials lead to the development of next-generation *ALK* TKIs with a higher CNS penetration.

#### Second-Generation TKIs

**Alectinib.** Alectinib has activity against the most common crizotinib-resistant mutations. It was first approved in the crizotinib-resistance setting.<sup>32,33</sup> In patients with crizotinib refractory disease, a pooled analysis of CNS response to alectinib in two phase II studies revealed a CNS RR of 64% in patients with measurable disease.<sup>34</sup> In the ALUR (ClinicalTrials.gov identifier: [NCT02604342](#)) phase III trial of alectinib versus chemotherapy in crizotinib-pretreated patients, the CNS RR for alectinib in those with measurable disease was 54.2%.<sup>35</sup>

In the treatment-naïve setting, alectinib has demonstrated superior CNS activity compared with crizotinib in the ALEX (ClinicalTrials.gov identifier: [NCT02075840](#)) and J-ALEX trials. In the alectinib and crizotinib arms, the CNS overall response rates were 81% and 50%, respectively, and the CNS durations of response (DOR) were 17.3 and 5.5 months, respectively. Patients with previously irradiated brain disease had higher intracranial RR (86% v 79%) and intracranial DOR (not reached v 17.3 months) compared

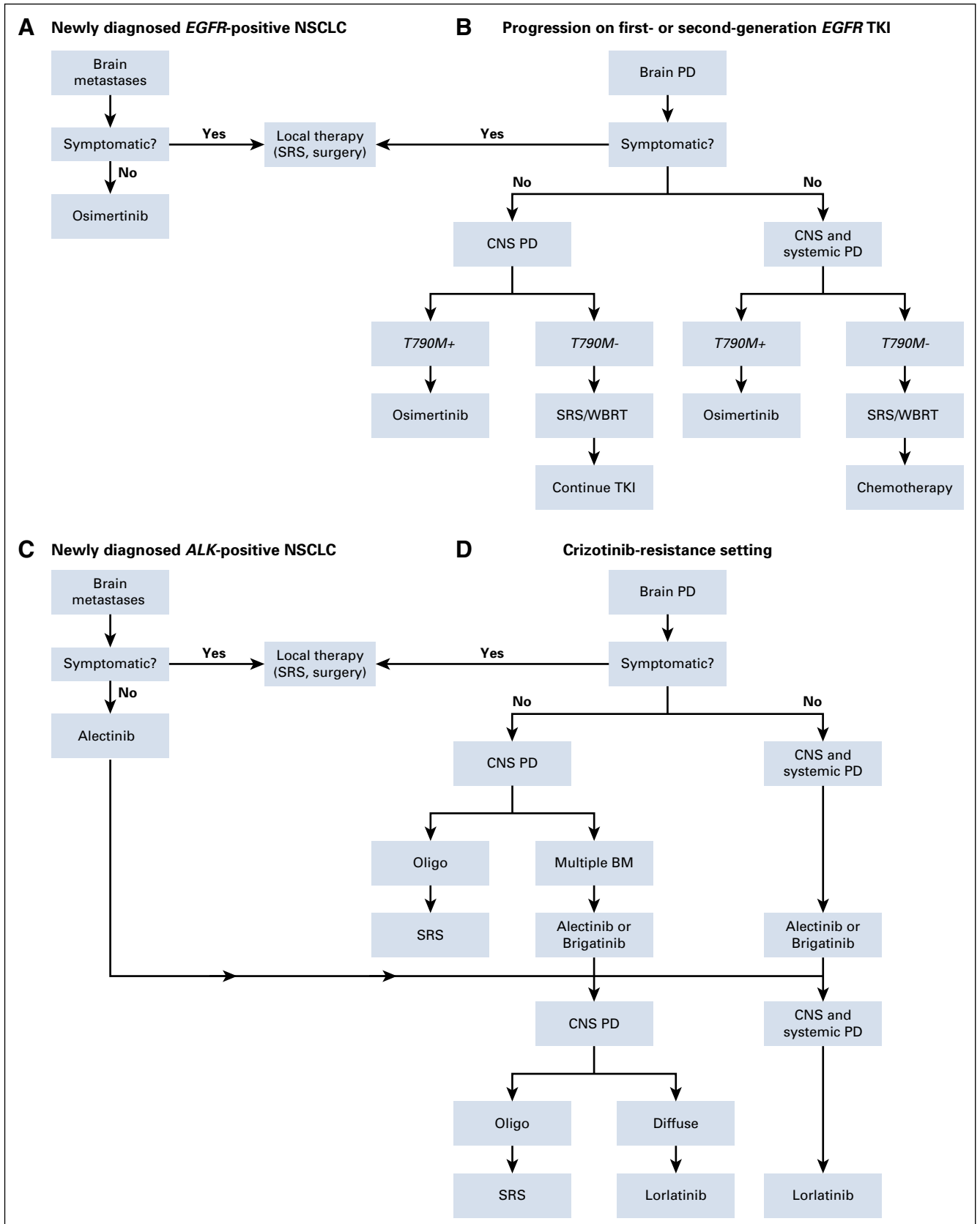
with patients without previous radiotherapy.<sup>36</sup> Similar results were observed in the Japanese population of the J-ALEX trial, but the BMs were not a stratification factor, so there was an imbalance in the prevalence of BMs in the two arms.<sup>37,38</sup> The cumulative rate of CNS progression (with adjustment for the competing risks of non-CNS progression and death) in the ALEX trial favored alectinib, and the 12-month CNS progression rates in the alectinib and crizotinib arms were 9.4% and 41.4%, respectively. An update of the ALEX trial showed median PFS of 27.7 months and 7.4 months in patients with baseline CNS metastases for alectinib and crizotinib, respectively.<sup>39</sup> These data demonstrate the activity of alectinib in treating BMs and the potential to delay and prevent the development of BMs. Of note, the ALEX international trial used an alectinib dose of 600 mg twice per day, and the Japanese trial used a dose of 300 mg twice per day. It is not known whether there is a relationship between CNS activity and dose.

A retrospective study recently evaluated alectinib in *ALK*-positive disease with large ( $\geq 1$  cm) or symptomatic CNS metastases. The majority of the patients received one previous TKI. CNS RR was 73.3%, CNS disease control rate was 100%, and CNS DOR was 19.3 months. All patients with neurologic symptoms improved after starting the TKI. Alectinib may be a reasonable option even for patients with larger metastases and symptomatic CNS disease.<sup>40</sup>

**Brigatinib.** Brigatinib is a highly potent *ALK*TKI with activity against *ROS1* and *T790M*-positive disease. It has a broader range of activity against crizotinib-resistant mutations compared with alectinib. Initially, brigatinib was approved in the crizotinib-refractory setting.<sup>41</sup> Subsequently, a phase III trial demonstrated the superiority of brigatinib to crizotinib in treatment-naïve patients.<sup>42</sup>

In the crizotinib-resistance setting, an exploratory analysis of a phase I/II and a phase II trial (ALTA; ClinicalTrials.gov identifier: [NCT02094573](#)) revealed an intracranial RR of 53% in the phase I/II study, and 67% in the arm with 180 mg/day dosing with a 7-day lead-in at 90 mg (arm B) of the ALTA study. The median intracranial PFS ranged from 14.6 to 18.4 months.<sup>43</sup> In the treatment-naïve setting, for patients with measurable disease, the ALTA-1L (ClinicalTrials.gov Identifier: [NCT02737501](#)) trial revealed an intracranial RR of 78% in the brigatinib group versus 29% in the crizotinib group. Brigatinib was associated with a lower rate of intracranial disease progression compared with crizotinib (19% v 9%, respectively). We anticipate that brigatinib will soon receive FDA approval in the first-line setting.

**Ceritinib.** Ceritinib is a second-generation TKI with activity against *ALK* and *ROS1*. In patients with crizotinib refractory disease, the ASCEND-5 (ClinicalTrials.gov identifier: [NCT01828112](#)) trial compared ceritinib to chemotherapy. In patients with BMs, the PFS was 4.4 months in the ceritinib group versus 1.5 months in the chemotherapy



**FIG 1.** Management of brain metastases (BMs) in (A-B) EGFR-positive and (C-D) ALK-positive non-small-cell lung cancer (NSCLC). Oligo, oligometastatic; PD, progressive disease; SRS, stereotactic radiosurgery; TKI, tyrosine kinase inhibitor; WBRT, whole-brain radiation therapy.

group. The intracranial RR in patients with measurable disease was 35%, and the median DOR was 6.9 months in the ceritinib arm.<sup>44</sup> The ASCEND-2 (ClinicalTrials.gov identifier: [NCT01685060](https://clinicaltrials.gov/ct2/show/study/NCT01685060)) trial demonstrated a similar intracranial RR of 33%; median DOR was 9.2 months and intracranial PFS was 5.4 months.

In treatment-naïve patients, the ASCEND-4 (ClinicalTrials.gov identifier: [NCT01828099](https://clinicaltrials.gov/ct2/show/study/NCT01828099)) study compared first-line ceritinib with chemotherapy. The intracranial RR was 72.7% for ceritinib and 27% for chemotherapy in patients with measurable disease. The PFS for those with BMs was 10.7 months in the TKI group versus 6.7 months in the chemotherapy group. The median duration of intracranial response was 16.6 months in the ceritinib group.<sup>28</sup> Despite the level of CNS activity of ceritinib, this agent is used less frequently because of a higher rate of GI adverse events.

### Third-Generation TKI

**Lorlatinib.** Lorlatinib is a highly potent, brain-penetrant TKI that inhibits *ALK*, *ROS1*, and most of the *ALK* resistance mutations, including *Gly1202Ar*. On the basis of the results of a phase I trial in a pretreated *ALK*-positive and *ROS1*-rearranged patient population, the FDA approved lorlatinib in the third- and second-line settings (after alectinib or ceritinib failure).<sup>45</sup> In the subsequent phase II trial, lorlatinib achieved an intracranial RR of 66.7% in treatment-naïve patients, 87% in crizotinib-refractory patients, 53.1% in those who received two or more TKIs, and 63% in those who received at least one previous *ALK* TKI.<sup>46</sup> Besides its efficacy, one of the most important aspects of lorlatinib is its activity against the *Gly1202Ar* resistance mutation, which may develop after a second-generation TKI. Lorlatinib is the only systemic therapy that may salvage patients who experience CNS progression after alectinib or brigatinib.

In summary, in patients with newly diagnosed *ALK*-positive NSCLC and symptomatic BMs, we recommend local therapy (SRS, surgery) followed by alectinib. For those with asymptomatic BMs, we recommend alectinib as first-line therapy (Fig 1C). In patients with symptomatic BMs that progressed on crizotinib, we recommend local therapy for symptomatic CNS disease followed by alectinib or brigatinib. For patients with disease progression on crizotinib and asymptomatic BMs, we recommend alectinib or brigatinib (Fig 1D).

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### ROS-1-REARRANGED NSCLC

*ROS1*-positive disease occurs in approximately 1% to 2% of patients with NSCLC. The incidence of BMs in this subgroup of patients is widely variable, ranging from 3.2% to 36%.<sup>47,48</sup> Crizotinib is approved by the FDA for *ROS1*-positive disease, and ceritinib has shown activity in this patient population. Approximately 30% of patients are expected to develop CNS metastases during treatment with crizotinib.<sup>49</sup> The largest study of crizotinib in *ROS1*-positive disease did not evaluate intracranial RR. The median PFS was shorter in patients with BMs. Thus, the activity of crizotinib in patients with *ROS1*-rearranged tumors and BMs remains largely unknown.

In a phase II study, ceritinib demonstrated an intracranial RR of 25%.<sup>50</sup> Lorlatinib was evaluated in this population, and the intracranial RR was 53% in crizotinib-pretreated patients and 66.7% among the crizotinib-naïve patients.<sup>45</sup> In patients with *ROS1*-positive disease and symptomatic BMs, we recommend local therapy followed by crizotinib. In those with small and asymptomatic BMs, it is reasonable to start crizotinib and monitor the intracranial disease. In patients with multiple or large BMs, we recommend local therapy followed by crizotinib.

In conclusion, the treatment of NSCLC has changed dramatically over the last few years. Biomarker-directed therapy improves CNS response, systemic response, QoL, PFS, and sometimes even OS. In asymptomatic patients with BMs, first-line TKIs may defer local treatment and delay CNS progression. Consequently, it is crucial to perform broad molecular testing in every patient with metastatic nonsquamous NSCLC. Liquid biopsy is emerging as an easy and fast method of detecting targetable alterations and evaluating resistance mechanisms to TKIs. The efficacy of checkpoint inhibitors in patients with BMs is modest; however, the data are still quite limited. In patients with no driver alterations, we recommend surveillance for those with small and asymptomatic BMs and local therapy followed by systemic therapy for those with symptomatic or multiple BMs. We anticipate that the treatment of patients with NSCLC will continue to evolve at an accelerated pace. The future of patients with NSCLC is looking brighter than ever before.

### 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/JOP.19.00357>.

## AUTHOR CONTRIBUTIONS

**Conception and design** All authors  
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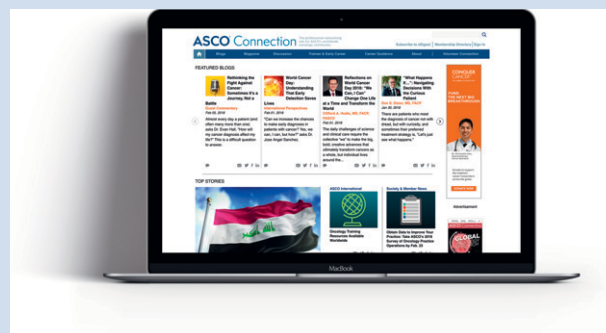
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**AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**Management of Brain Metastases in Non-Small-Cell Lung Cancer**

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