Central nervous system (CNS) metastases remain a significant problem in the management of patients with ALK-rearranged non-small cell lung cancer (NSCLC). The frequency of CNS involvement in ALK-positive tumors is extremely high; it approaches 25% in treatment-naive patients (1) and rises to 50% in patients treated with crizotinib (2,3). Crizotinib was previously reported to have only minor intracranial activity (4), with poor CNS penetration suggested as the underlying mechanism (5).

The study published this year by Solomon and colleagues in Journal of Clinical Oncology addressed the question of intracranial efficacy of crizotinib in PROFILE 1014 trial (1). The study confirmed that crizotinib, as compared with platinum-based chemotherapy, is associated with better progression-free survival (PFS) irrespectively of presence or absence of brain metastases at the time of initial diagnosis [HR 0.4 (0.23–0.29); P<0.001] and 0.51 (0.38–0.69; P<0.001) for patients with and without CNS metastases, respectively. Most importantly, the results hinted towards better control of intracranial disease with crizotinib as compared to platinum-based chemotherapy. The effect was even more pronounced in patients with brain metastases at study entry. Is it a pure statistical phenomenon? Imbalances in the baseline patient characteristics, such as male predominance in the CNS metastases subgroup, cannot be responsible for the differences observed. Differences in the schedule assessment between the subgroups may have confounded the results. However, the most possible explanation for larger effect observed with crizotinib in patients with brain metastases treated with RT before the study entry as opposed to patients without CNS metastases is better drug penetration into the CNS resulting from the disruption of the blood-brain barrier by the brain irradiation. Of note, the results observed in that subgroup are in line with the results of the combined analysis of PROFILE 1005 and PROFILE 1007 studies, confirming higher CNS control rate achieved with brain irradiation (4). Solomon and colleagues were first to demonstrate that better CNS control is not a pure radiation effect (since both arms received brain irradiation), but the effect of the combination, supporting the hypothesis of drug penetration improvement.

Can the study published by Solomon and colleagues provide us with a “yes or no” answer with regards to intracranial efficacy of crizotinib? The answer to the question is no. It is important to emphasize that although IC-TTP was a protocol-specified end-point, the study was underpowered to demonstrate a statistically significant difference in intracranial effects between crizotinib and chemotherapy. In fact, only 15% of the ITT population had their disease progressed in the CNS. On the other hand, if the existing difference is too small to be picked-up in a large-size cohort study—whether that amount of effect we are looking for in clinics?

Interestingly enough, the intracranial effect of crizotinib was more pronounced in patients with brain metastases at study entry. Is it a pure statistical phenomenon? Imbalances in the baseline patient characteristics, such as male predominance in the CNS metastases subgroup, cannot be responsible for the differences observed. Differences in the schedule assessment between the subgroups may have confounded the results. However, the most possible explanation for larger effect observed with crizotinib in patients with brain metastases treated with RT before the study entry as opposed to patients without CNS metastases is better drug penetration into the CNS resulting from the disruption of the blood-brain barrier by the brain irradiation. Of note, the results observed in that subgroup are in line with the results of the combined analysis of PROFILE 1005 and PROFILE 1007 studies, confirming higher CNS control rate achieved with brain irradiation (4). Solomon and colleagues were first to demonstrate that better CNS control is not a pure radiation effect (since both arms received brain irradiation), but the effect of the combination, supporting the hypothesis of drug penetration improvement.

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following brain RT. Indeed, higher peak (Cmax) crizotinib concentrations in the cerebro-spinal fluid (CSF) may provide a prolonged CNS control in ALK-rearranged tumors (6-8).

Importantly, another scenario of combining RT with crizotinib in order to achieve intracranial control is administration of cranial irradiation after isolated intracranial progression which allows controlling the disease for another 5–7 months (1,4,9).

Overall, crizotinib used as a sole modality has modest intracranial activity and is only marginally superior to chemotherapy in terms of intracranial disease control. Furthermore, its intracranial effects require brain irradiation to be given at some point in the majority of cases in order to control the disease in the CNS. Whole brain radiation therapy (WBRT), on the other hand, delivered early in the disease course frequently results in long-term cognitive decline and substantial neurological morbidity (10).

New-generation ALK-inhibitors not only have a broader spectrum of activity in terms of resistant mutations in the ALK gene but also possess better CNS penetration. In particular, alectinib administered at a standard dose produces therapeutic concentrations in the CSF (11). Although the data with regards to intracranial activity of newer compounds is limited, it is very promising (Table 1). Thus, new generation ALK-inhibitors might represent a better alternative to RT in case of intracranial progression during crizotinib treatment (8). Furthermore, it is very possible that new-generation ALK-inhibitors are superior to crizotinib in treatment-naïve patients. According to the results of J-ALEX, a Japanese phase III randomized trial evaluating alectinib versus crizotinib in advanced ALK-positive NSCLC patients naïve to ALK-tyrosine kinase inhibitors (TKI), alectinib is superior to crizotinib in terms of PFS (19). The results of ALEX trial having the same design and conducted in the Caucasian population are highly awaited. Noteworthy, permitting patients with asymptomatic CNS metastases and having time-to-CNS progression as a key secondary end-point, ALEX trial is expected to provide important prospective data on the comparative intracranial efficacy of the two agents.

Acknowledgements
None.

Footnote
Provenance: This is a Guest Commentary commissioned by Section Editor Shaohua Cui (Department of Pulmonary Medicine, Shanghai Chest Hospital, Shanghai Jiao Tong University, Shanghai, China).
Conflicts of Interest: Elizabeth Dudnik—honoraria for

Table 1 Intracranial response to different ALK-TKI in patients with ALK-rearranged NSCLC and measurable brain metastases

<table>
<thead>
<tr>
<th>ALK TKI</th>
<th>Study (references)</th>
<th>Brain RT (administered in &gt;50% of pts)</th>
<th>No brain RT/CNS progression after brain RT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ORR (%) RECIST 1.1</td>
<td>CRR (%) RECIST 1.1</td>
<td>ORR (%) RECIST 1.1</td>
</tr>
<tr>
<td></td>
<td>[pts evaluated, n]</td>
<td>[pts evaluated, n]</td>
<td>[pts evaluated, n]</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>PROFILE 1005+; PROFILE 1007 (4)</td>
<td>33 [18] NR</td>
<td>18 [22] NR</td>
</tr>
<tr>
<td></td>
<td>ASCEND-2 (13)</td>
<td>NR NR 39 [33]* 3 [33]*</td>
<td></td>
</tr>
<tr>
<td>Alectinib</td>
<td>NP28671 (14)</td>
<td>75 [16] 25 [16]</td>
<td>— —</td>
</tr>
<tr>
<td></td>
<td>NP28671+ NP28673 combined analysis (16)</td>
<td>60 [50] 14 [50]</td>
<td>— —</td>
</tr>
<tr>
<td>Lorlatinib</td>
<td>Solomon et al. (18)</td>
<td>39 [18] 28 [18]</td>
<td>— —</td>
</tr>
</tbody>
</table>

*, new/progressing brain metastases after brain irradiation; ¥, brigatinib 180 mg/d; ¥¥, brigatinib 90 mg/d; CRR, complete response rate; NR, not reported; ORR, overall response rate; pts, patients; RECIST 1.1, Response Evaluation Criteria in Solid Tumors, version 1.1; RT, radiotherapy; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung cancer.

References

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