Management of Leptomeningeal Metastatic Disease in ALK-Positive NSCLC

Kathryn Willoughby, MD
Medical University of South Carolina
August 8, 2015
Off-Label Use Disclosure(s)

- I do not intend to discuss an off-label use of a product during this activity.
Financial Disclosure(s)

- I have not had any relevant financial relations during the past 12 months to disclose.
Clinical Presentation

- 50-year-old, otherwise healthy, gentleman with minimal remote smoking history presented to PCP with right sided chest pain
- CT imaging showed consolidation
- antibiotics, inhalers, prednisone
- Worsening dyspnea over months lead to repeat CT imaging
- Right pleural effusion, focal septal thickening in the right upper lobe, enlarging sclerotic focus in the right lateral sixth rib
- Thoracentesis cytology positive for adenocarcinoma and tested positive for ALK re-arrangement
- Initial MRI negative for intracranial disease
Treatment

- Crizotinib started with favorable response
- Discontinued secondary to Grade 4 transaminitis
- Second-line: carboplatin/pemetrexed x 4 cycles
- Maintenance pemetrexed x 2 cycles
- Referral to Massachusetts General Hospital – Enrolled in Phase II clinical trial with LDK 278, second generation ALK inhibitor (ceritinib)
Treatment Timeline

- Diagnosis
- Start crizotinib
- crizotinib stopped
- Start Carbo/Pem
- Completed 4 cycles: Pem maintenance
- Progressive Disease
- LDK 278 Clinical Trial
- Intracranial disease diagnosed: gamma knife x 8 targets
- Gamma knife x 10 targets
- WBRT
- Progressive Disease
- Identify LM
- Alectinib started

Dates:
- March 2012
- April 2012
- September 2012
- December 2012
- January 2013
- February 2013
- September 2013
- October 2013
- November 2013
- February 2014
LM Response

Pre-alectinib

8 weeks post alectinib
Response Duration

- Started March 25, 2014
- Remarkable clinical response
- Response until September 2014
- Enrolled in hospice
- Expired October 2014
Alectinib Salvages CNS Relapses in ALK-Positive Lung Cancer Patients Previously Treated with Crizotinib and Ceritinib

Justin F. Gainor, MD,* Carol A. Sherman, MD,† Kathryn Willoughby, MD,† Jennifer Logan, NP, MS,* Elizabeth Kennedy,* Priscilla K. Brastianos, MD,*† Andrew S. Chi, MD, PhD,‡ and Alice T. Shaw, MD, PhD*
### TABLE 1. Baseline Characteristics of ALK-Positive Patients with Leptomeningeal Metastases

<table>
<thead>
<tr>
<th>Pt.</th>
<th>Age</th>
<th>Sex</th>
<th>Prior ALK Inhibitors</th>
<th>Previous Radiation Therapy</th>
<th>Interval from Diagnosis to Development of LM</th>
<th>Concomitant Brain Metastases</th>
<th>Neurologic Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>56</td>
<td>M</td>
<td>Crizotinib, ceritinib</td>
<td>WBRT</td>
<td>23 Months</td>
<td>Yes</td>
<td>Seizure, confusion, word-finding difficulties</td>
</tr>
<tr>
<td>2</td>
<td>50</td>
<td>M</td>
<td>Crizotinib, ceritinib</td>
<td>Radiosurgery × 2, WBRT</td>
<td>18 Months</td>
<td>Yes</td>
<td>Headaches, diplopia, slurred speech, nausea, ptosis</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>F</td>
<td>Crizotinib, ceritinib</td>
<td>WBRT</td>
<td>9 Months</td>
<td>No</td>
<td>Focal seizures, right-sided weakness, visual hallucinations</td>
</tr>
<tr>
<td>4</td>
<td>49</td>
<td>F</td>
<td>Crizotinib, ceritinib</td>
<td>None</td>
<td>16 Months</td>
<td>Yes</td>
<td>Fatigue</td>
</tr>
</tbody>
</table>

ALK, anaplastic lymphoma kinase; F, female; LM, leptomeningeal metastases; M, male; WBRT, whole brain radiation therapy.

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<table>
<thead>
<tr>
<th>Pt.</th>
<th>Response</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Yes</td>
<td>5 months, continued</td>
</tr>
<tr>
<td>2</td>
<td>Yes</td>
<td>5 months</td>
</tr>
<tr>
<td>3</td>
<td>Yes</td>
<td>6 weeks, continued</td>
</tr>
<tr>
<td>4</td>
<td>Yes</td>
<td>4 months</td>
</tr>
</tbody>
</table>
Leptomeningeal Metastasis in NSCLC

- Dismal prognosis (median survival 3.0–4.3 months)
- Exclusion from clinical trials; thus, data on management largely retrospective data
- Treatment strategies include: WBRT, gamma knife, intra-thecal or systemic chemotherapy, pulsatile EGFR inhibition
Leptomeningeal Metastasis in ALK-Positive NSCLC

- 26% of ALK-positive patients with newly diagnosed, metastatic disease have CNS metastases
- 4% with LM
- Crizotinib, 12-week intracranial disease control rate of 56%
- 7% of patients have objective intracranial responses
- Rates of CNS metastasis as high as 60% in patients on trials for second-generation ALK inhibitors
Leptomeningeal Metastasis in ALK-Positive NSCLC

- Common site of relapse despite continued systemic disease control
- CSF-to-plasma ratio of crizotinib was very low (0.0026)
- High-dose crizotinib (1000mg once daily) or high-dose crizotinib (600mg once daily) plus pemetrexed (900mg/m2) in patients with brain metastases
- Crizotinib combined with intrathecal methotrexate
Second-generation ALK inhibitors in Leptomeningeal Metastasis

● Alectinib
  ● High brain-to-plasma ratios (0.63–0.94)
  ● P-glycoprotein (P-gp)
  ● objective responses in 55% of crizotinib-resistant/intolerant patients
  ● 21 patients with baseline CNS lesions
  ● 52% had objective responses in the CNS
  ● measurable concentrations of alectinib in CSF sampling

● ALK inhibitor AP26113
  ● 10 of 14 patients (71%) with untreated/progressive brain metastases experienced intracranial response

● Ceritinib
  ● Intracranial responses were seen in 10 of 29 patients (34.5%)
  ● CNS concentrations of ceritinib are predicted to 15% of plasma levels
Future Directions

- ALEX Study: This phase III randomized trial is evaluating first-line crizotinib versus alectinib in treatment-naive, ALK-positive lung cancer patients (NCT02075840)
  - time to CNS progression is a key secondary endpoint of the study

- PF-06463922 is a novel ALK inhibitor
  - antitumor activity in the CNS
  - strong activity against all known ALK resistance mutations identified in patients with crizotinib-resistant disease


