FLASCO SPRING SESSION 2019
Case presentation
LUNG CANCER SESSION

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Case Presentation

60 year old male, lifetime never smoker presented to an outside hospital with 2 week history of cough and chest discomfort.

- CT Angiogram to rule out PE showed a RUL mass, mediastinal LAD (right paratracheal and subcarinal) and 2 lesions in the 5th and 6th anterior ribs concerning for metastatic disease.
ANATOMICAL PATHOLOGY
- EBUS of the subcarinal LN showed adenocarcinoma from lung primary

MOLECULAR PATHOLOGY
- Tumor Pyrosequencing showed a EGFR exon 19 E746-A750 mutation
- The specimen was tested negative for KRAS, BRAF, ROS1, RET, ALK, MET or NTRK mutations
- PD-L1 IHC TPS was 50%
**Initial Staging**

- **PET CT**: Metabolically active RUL mass, right hilar and mediastinal (precarinal, subcarinal, right azygo-esophageal LAP), right thoracic pleural metastases with involvement of the right posterolateral fifth and sixth rib, and metabolic activity in the left superior acetabulum

- **MRI brain**: Negative for intracranial metastasis
Patient was started on first line therapy with EGFR TKI afatinib in January 2017

Restaging scans on afatinib showed PR

Approximately 10 months after starting afatinib, he developed persistent headache and gait imbalance.

Restaging imaging in October 2017 showed new brain lesions (right frontal lobe and cerebellum) and systemic progression of disease

Plasma Guardant 360 testing revealed a new EGFR T790M mutation and persistent EGFR exon 19 del.

Patient was started on osimertinib at 80mg/day for progressive disease in early November 2017.
Intracranial disease control on osimertinib

MRI brain with and without contrast. Left side images are prior to initiation of osimertinib. Right side images show response to treatment with osimertinib.
Restaging CT scans after 10 months of therapy with Osimertinib, in September 2018 showed systemic progression of disease.

CT guided biopsy of a new left iliac soft tissue mass was TTF-1, synaptophysin, chromogranin and CD56 positive, Napsin A and P40 negative, concerning for small cell carcinoma.

Molecular testing: Plasma Guardant 360 testing showed that the EGFR T790M mutation was not detectable and there was new MYC, PIK3CA and BRAF amplification and new TP53 V218L and G226S mutation.
Progression of disease on osimertinib

September 2018

June 2018

CT chest/Abdomen/pelvis with contrast, Left side images are on osimertinib with response to therapy, Right side images show progression of disease on osimertinib
DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.

- Mechanisms of resistance to osimertinib

- Treatment after progression on osimertinib
DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.

- Mechanisms of resistance to osimertinib

- Treatment after progression on osimertinib
Intracranial activity of Osimertinib at 160mg/ day dose

**BLOOM Study Design: Osimertinib LM Cohort 1**

Study objectives, cohort 1—EGFRm NSCLC and LM:
To assess the safety and tolerability of osimertinib in patients with LM

First patient dosed: April 14, 2015
Data cut-off: March 10, 2016

<table>
<thead>
<tr>
<th>Osimertinib LM cohort 1</th>
<th>Assesments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advanced or metastatic EGFRm NSCLC and confirmed diagnosis of LM by positive CSF cytology</td>
<td>Adverse events’</td>
</tr>
<tr>
<td>Key inclusion criteria:</td>
<td>Efficacy assessment:</td>
</tr>
<tr>
<td>• Primary tumor with EGFR L858R or exon 19 deletion</td>
<td>– OS</td>
</tr>
<tr>
<td>• Prior EGFR-TKI treatment</td>
<td>– Brain MRI and extracranial MRI or CT scan¹</td>
</tr>
<tr>
<td>• ECOG PS 0–2</td>
<td>– CSF cytology</td>
</tr>
<tr>
<td>• Stable extracranial disease</td>
<td>– Neurological exam’</td>
</tr>
<tr>
<td>• At least one LM lesion by MRI scan</td>
<td>– CNS symptoms’</td>
</tr>
</tbody>
</table>

Osimertinib 160 mg qd

¹As assessed by study investigator; modified RECIST for CNS disease; RECIST 1.1 for extracranial disease; CT/MRI, CSF cytology and neurological exam frequency every 6 weeks; 1 cycle = 21 days of continuous dosing.

CSF, cerebrospinal fluid; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group Performance Status; MRI, magnetic resonance imaging; RECIST, Response Evaluation Criteria In Solid Tumors


Adapted from https://www.primeoncology.org
Intracranial activity of Osimertinib 160mg/day dose

Osimertinib Activity Across LM Assessments

Efficacy assessments were conducted on 21 patients

- Seven patients had confirmed radiological improvement
- Two patients had confirmed CSF cytology clearance; no tumor cells were detected in two consecutive CSF samples
- Five patients had confirmed improved neurological function

<table>
<thead>
<tr>
<th>Best MRI Imaging</th>
<th>N = 21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intracranial</td>
<td></td>
</tr>
<tr>
<td>Response, n (%)</td>
<td>Confirmed</td>
</tr>
<tr>
<td>Responding</td>
<td>7 (33)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>9 (43)</td>
</tr>
<tr>
<td>Early withdrawal</td>
<td>2 (10)</td>
</tr>
</tbody>
</table>

Population: efficacy, n = 21. *Response confirmation was done at least 4 weeks after the initial response; †Response assessed by neurological examination

Intracranial activity of Osimertinib at 80mg/day dose

Osimertinib for patients (pts) with leptomeningeal metastases (LM) associated with EGFRm advanced NSCLC

- EGFR T790M-positive advanced NSCLC with asymptomatic, stable CNS metastases, including leptomeningeal disease across AURA studies
- 22 pts with leptomeningeal disease (LM).
- ORR was 55% (95% CI 32, 76).
  - Complete LM response and partial LM response reported in 6 pts (27%) each.
- Median LM DoR for confirmed responders was not calculable (range 1.3–11.1 mo).
- Median LM PFS was 11.1 mo (95% CI 4.6, NC).
- Median OS was 18.8 mo (95% CI 6.3, NC).

Presented by Ahn et al. European Society of Medical Oncology, Asia 2018 Congress
CNS Response to Osimertinib Versus Standard Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Patients With Untreated EGFR-Mutated Advanced Non–Small-Cell Lung Cancer


Table 3. CNS Response to Osimertinib Versus Standard EGFR-TKIs

<table>
<thead>
<tr>
<th>Response</th>
<th>Osimertinib (n = 61)</th>
<th>Standard EGFR-TKIs (n = 67)</th>
<th>Osimertinib (n = 22)</th>
<th>Standard EGFR-TKIs (n = 19)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>26 (43)</td>
<td>16 (24)</td>
<td>10 (45)</td>
<td>5 (26)</td>
</tr>
<tr>
<td>PR</td>
<td>15 (25)</td>
<td>13 (19)</td>
<td>6 (27)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>SD &lt; 6 weeks†</td>
<td>15 (25)</td>
<td>27 (40)</td>
<td>1 (5)</td>
<td>4 (21)</td>
</tr>
<tr>
<td>PD</td>
<td>0</td>
<td>5 (7)</td>
<td>0</td>
<td>2 (11)</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>6 (10)</td>
<td>6 (9)</td>
<td>1 (5)</td>
<td>0</td>
</tr>
<tr>
<td>CNS DCR, No. (%)</td>
<td>55 (88)</td>
<td>56 (84)</td>
<td>21 (95)</td>
<td>17 (89)</td>
</tr>
<tr>
<td>96% Ctr</td>
<td>80 to 96</td>
<td>73 to 92</td>
<td>77 to 100</td>
<td>67 to 99</td>
</tr>
<tr>
<td>OR (%)</td>
<td>0.9 to 5.5</td>
<td>2.5</td>
<td>0.2 to 5.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Median time to response, weeks (interquartile range)</td>
<td>6 (8-12)</td>
<td>6 (8-12)</td>
<td>6 (8-12)</td>
<td>6 (8-12)</td>
</tr>
<tr>
<td>Estimated % remaining in response (95% CI)**</td>
<td>1.8</td>
<td>.269</td>
<td>.82</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CR, complete response; DCR, disease control rate; EFR, epidermal growth factor receptor; CI, not calculable; NR, not reached; 95% CI, 95% confidence interval; NR, not calculable; ORR, objective response rate; PD, progressive disease; SD, stable disease; TKI, tyrosine kinase inhibitor.

*Responses did not require confirmation, per RECIST 1.1 guidance on randomized studies.
†Includes non-CR, non-PD in patients with nonpalpable lesions only.
‡Calculated using Clopper-Pearson exact method for binomial proportions.
§This analysis was performed using logistic regression with a factor for treatment; CI was calculated using profile likelihood. An OR > 1 favors osimertinib.

The Probit was calculated based on the likelihood ratio test, which compared two models: one model with the intercept only and a second model including the treatment factor.

![Graphs showing CNS Progression-Free Survival and Remaining in Response](image-url)
DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.

  - **Mechanisms of resistance to osimertinib**

  - Treatment after progression on Osimertinib
• Retrospective study

• Sample: Tissue from EGFR T790Mm+ NSCLC patients on commercially available osimertinib and plasma samples from Phase 1 AURA trial validation cohort.

• Genomic profiling analysis of post osimertinib progression tumor tissue by NGS and plasma by digital PCR

• Time to treatment discontinuation was significantly lower in the T790M loss vs T790M preserved group (6.1 vs. 15.2 months, p value = 0.01)

Oxnard et al. JAMA Oncology 2018
RESISTANCE TO OSIMERTINIB IN PATIENTS WITH EGFR T790M MUTATION
MOFFITT AND MD ANDERSON EXPERIENCE, N=118

Blue box: Mutations
Red box: Amplification
Purple box: Mutation and/or amplification GM: Denovo (Suspected germline) EGFR T790M mutation with VAF ~50%

Le, Puri et al. Clinical Cancer Research December 2018
**FIG 1.** Time to event analyses. (A) Time since diagnosis to transformation to small-cell lung cancer (SCLC) and overall survival (OS) since the time of diagnosis. (B) Progression-free survival (PFS) of SCLC-transformed patients treated with platinum-etoposide. (C) PFS of SCLC-transformed patients treated with taxanes. (D) OS since the time of SCLC transformation.

**TABLE 3.** Frequency of Common Mutations Within Small-Cell Lung Cancer Cases, by Testing Method

<table>
<thead>
<tr>
<th>Genotyping Platform</th>
<th>TP53</th>
<th>RB1</th>
<th>PIK3CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>All assays</td>
<td>38/48 (79)</td>
<td>18/31 (58)</td>
<td>14/52 (27)</td>
</tr>
<tr>
<td>Allele-specific PCR</td>
<td>2/8 (25)</td>
<td>—</td>
<td>3/8 (38)</td>
</tr>
<tr>
<td>NGS</td>
<td>32/35 (91)</td>
<td>15/26 (58)</td>
<td>11/39 (28)</td>
</tr>
<tr>
<td>Whole-exome sequencing</td>
<td>3/4 (75)</td>
<td>3/4 (75)</td>
<td>0/4 (0)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1/1 (100)</td>
<td>0/1 (0)</td>
<td>0/1 (0)</td>
</tr>
</tbody>
</table>

**NOTE:** Data are given as No. (%). One case genotyped only by plasma cell-free DNA analysis is not included in this table (patient 53; Appendix Table A1).

Abbreviations: NGS, next-generation sequencing; PCR, polymerase chain reaction.
DISCUSSION

- Intracranial activity of osimertinib in minimally symptomatic patients/ asymptomatic patients with intracranial metastatic disease.

- Mechanisms of resistance to osimertinib

- Treatment after progression on osimertinib
FUTURE DIRECTIONS: TATTON TRIAL

- Multicenter, Multi arm phase I trial in patients with progression prior EGFR TKI.
- Osimertinib with ascending doses of
  - Savolitinib (AZD6094): cMET inhibitor or,
  - Selumitinib (MEK1/2 inhibitor) or,
  - Durvalumab (MEDI4736): PD-L1 inhibitor
- Phase IB dose expansion cohort
  - (osimertinib + savolitinib) in osimertinib naïve or pretreated EGFRm+ and cMET + patients*
  - ORR was 33% in cohort of patients with prior T790M directed therapy
  - AE ≥ Grade 3 in 50% (33/66) pts, AE leading to death 6% (4/66), 40% (27/66) drug discontinuation due to AEs
  - PD-L1 combination therapy arm on hold due higher incidence of interstitial lung disease

*MET-positive status was to be confirmed centrally by fluorescence in-situ hybridisation (FISH; MET gene copy ≥5 or MET/CEP7 ratio ≥2). Patients were allowed to be enrolled based on local FISH, immunohistochemistry (IHC; +3 in ≥50% of tumour cells), or NGS


TATTON: A Multi-arm, Phase Ib, Open-Label, Multicentre Study to Assess the Safety, Tolerability, Pharmacokinetics and Preliminary Anti-tumour Activity of AZD9291 in Combination With Ascending Doses of Novel Therapeutics in Patients With EGFRm+ Advanced NSCLC Who Have Progressed Following Therapy With an EGFR TKI

Preliminary anti-tumour activity in all MET-positive patients*, n = 64

<table>
<thead>
<tr>
<th>Objective response rate, n (%)</th>
<th>Prior 3rd Gen T790M directed EGFR-TKI (n = 30)</th>
<th>No prior 3rd Gen T790M directed EGFR-TKI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR†</td>
<td>10 (33)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>T790M+ (n = 11)</td>
<td>14 (61)</td>
<td>30 (47)</td>
</tr>
<tr>
<td>T790M- (n = 23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (n = 64)</td>
<td></td>
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</tr>
</tbody>
</table>

**Waterfall plot based on evaluable patients (n = 64); all patients treated with on-treatment assessment or discontinuation prior to first tumour assessment. Data as of 31 Aug 2017**

*17 patients did not have central FISH confirmation of MET-positive status (n = 5 MET-negative; k = 11 unknown by central lab). †Confirmed by a later scan performed at least 4 weeks after initial response observed

TATTON Part 2 NCT02914346
Monotherapy with immune checkpoint inhibitors in the 2nd line setting does not improve survival in patients with EGFRm+ NSCLC.

**IMPOWER150**
- Phase III trial
- Atezolizumab in combination with carboplatin+paclitaxel +/- bevacizumab (ACP +/-B) compared to carboplatin + paclitaxel +bevacizumab (BCP) in patients with non squamous NSCLC
- Subgroup of chemotherapy naïve patients with EGFR/ALK mutations have significantly higher PFS withABCP compared to BCP.

**Future chemo-immunotherapy trial**
- Carboplatin/Cisplatin plus pemetrexed with or without pembrolizumab in TKI resistant EGFR non squamous NSCLC (NCT03515837)
- Includes Osi naïve or pre treated patients with or without T790M mutation
TREATMENT AFTER PROGRESSION ON OSIMERTINIB
WHAT’ NEXT??

• Clinical trials with EGFR TKIs combinations
• Clinical trials with IO +/- chemotherapy combinations
• Chemotherapy + VEGF + Immunotherapy (IMPOWER150) trial
• Chemotherapy alone.
QUESTIONS??