Considerations for Choosing TKIs for Squamous NSCLC in the Era of Immunotherapy: Which Patients Could Benefit?

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Faculty Disclosure

- Honoraria: Boehringer Ingelheim, Merck, Eli Lilly, Bristol-Myers Squibb, Novartis, Pfizer, AstraZeneca
Squamous Cell Carcinoma (SqCC) of the Lung

- Squamous histology represents approximately 20–40% of NSCLC\textsuperscript{1,2}
- SqCC of the lung remains a disease with high unmet need
- SqCC of the lung is associated with poor prognosis\textsuperscript{3}
- Targetable oncogenic alterations are few
- Additional therapeutic options are needed

OS = overall survival; NSCLC = non-small cell lung cancer.

Current Treatment Recommendations for Metastatic SqCC of the Lung

Never or former light smoker (<15 pack/year) → Molecular test (ALK/EGFR) → Molecular test positive

Molecular test (ALK/EGFR) → Molecular test negative

Targeted therapy

I) Age
II) PS

<70 years and PS 0-1

4-6 cycles: Cisplatin – gemcitabine (I, A)
Cisplatin – docetaxel (I, A)
Cisplatin – vinorelbine (I, A)
Carboplatin – paclitaxel (I, A)
Carboplatin – nab-paclitaxel (I, B)
Cisplatin – gemcitabine – necitumumab (if EGFR expression by IHC) (I-B; MCBS 1)

<70 years and PS 2 or >70 years and PS 0-2

4-6 cycles: Carboplatin-based doublets (II, B)
Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) (I-A)

Stage IV SqCC

BSC (II, B)

PS 3–4

PS 0–2

Nivolumab (I, A; MCBS 5)
Pembrolizumab if PD-L1>1%
(I, A; MCBS 3 if PD-L1 >1%; MSBC 5 if PD-L1 >50%)
Docetaxel (I, B)
Ramucirumab – docetaxel (I, B; MCBS 2)
Erlotinib (II, C)
Afatinib (I, C; MCBS 1)

Disease progression

BSC

4-6 cycles:
Cisplatin – gemcitabine (I, A)
Cisplatin – docetaxel (I, A)
Cisplatin – vinorelbine (I, A)
Carboplatin – paclitaxel (I, A)
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Cisplatin – gemcitabine – necitumumab (if EGFR expression by IHC) (I-B; MCBS 1)

4-6 cycles:
Carboplatin-based doublets (II, B)
Single-agent chemotherapy (gemcitabine, vinorelbine or docetaxel) (I-A)


* ESMO guidelines do not recommend maintenance therapy in the treatment of squamous cell carcinoma NSCLC. 1 BSC = Best Standard of Care; EGFR = epidermal growth factor receptor; MCBS = Magnitude of Clinical Benefit Scale; NSCLC = non-small cell lung cancer; PD-L = programmed death-ligand; PS = Performance Status; SqCC = squamous cell carcinoma.
### Overview of Recent Key Phase III ≥ Second-line Treatment Studies in Patients With SqCC of the Lung

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>Median PFS (mo)</th>
<th>HR for PFS</th>
<th>Median OS (mo)</th>
<th>HR for OS</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>REVEL&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Ramucirumab + doce vs doce Squamous (n=328)</td>
<td>4.5 vs 3.0</td>
<td>0.76*</td>
<td>10.5 vs 9.1</td>
<td>0.86*</td>
<td>22.9 vs 13.6*</td>
</tr>
<tr>
<td></td>
<td>(n=1253)</td>
<td>4.2 vs 2.7</td>
<td>0.76*</td>
<td>9.5 vs 8.2</td>
<td>0.88</td>
<td></td>
</tr>
<tr>
<td>CheckMate-017&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Nivolumab vs doce All squamous (n=272)</td>
<td>3.5 vs 2.8</td>
<td>0.62*</td>
<td>9.2 vs 6.0</td>
<td>0.59*</td>
<td>20.0 vs 9.0*</td>
</tr>
<tr>
<td>KEYNOTE-010&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Pembrolizumab vs doce PD-L1 PS ≥50% (n=442) Squamous (n=222)</td>
<td>2 mg: 5.0 vs 4.1</td>
<td>0.59*</td>
<td>14.9 vs 8.2</td>
<td>0.54*</td>
<td>30.0 vs 8.0*</td>
</tr>
<tr>
<td></td>
<td>10 mg: 5.2 vs 4.1</td>
<td>10 mg: 5.2 vs 4.1</td>
<td>0.86</td>
<td>17.3 vs 8.2</td>
<td>0.50*</td>
<td>29.0 vs 8.0*</td>
</tr>
<tr>
<td>LUX-Lung 8&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Afatinib vs erlotinib Squamous (n=795) All squamous</td>
<td>2.6 vs 1.9</td>
<td>0.81*</td>
<td>7.9 vs 6.8</td>
<td>0.81*</td>
<td>6.0 vs 2.8*</td>
</tr>
<tr>
<td>OAK&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Atezolizumab vs doce Squamous (n=222)</td>
<td>2.8 vs 4.0</td>
<td>0.95</td>
<td>13.8 vs 9.6</td>
<td>0.73*</td>
<td>14 vs 13</td>
</tr>
<tr>
<td></td>
<td>(n=850)</td>
<td>NR for squamous</td>
<td>NR for squamous</td>
<td>8.9 vs 7.7</td>
<td>0.73*</td>
<td></td>
</tr>
</tbody>
</table>

All agents listed are FDA and EMEA approved for the treatment of SqCC of the lung.

*P<0.05.
doce = docetaxel; EMEA = European Medicines Agency; FDA = US Food and Drug Administration; HR = hazard ratio; mo = months; NR = not reported; ORR = objective response rate; OS = overall survival; PD-L1 = programmed death-ligand 1; PFS = progression-free survival; PS = proportion score; SqCC = squamous cell carcinoma.

ESMO Guidelines: Second-line Recommendations

Nivolumab (I, A; MCBS 5)
Pembrolizumab if PD-L1 >1%
(I, A; MCBS 3 if PD-L1 >1%; MSBC 5 if PD-L1 >50%)
Docetaxel (I, B)
Ramucirumab – docetaxel (I, B; MCBS 2)
Erlotinib (II, C)
Afatinib (I, C; MCBS 1)

MCBS = Magnitude of Clinical Benefit Scale; PD-L = programmed death-ligand.
SqCC of the Lung: Genetically Complex Malignancy

- High burden of somatic mutations/genomic alterations

- Overexpression/derangements of EGFR\textsuperscript{2,3}, HER2\textsuperscript{4,5}, HER4\textsuperscript{6} and/or dysregulation of their downstream pathways implicated in the pathogenesis of SqCC of the lung

ErbB Pathway is Frequently Dysregulated in SqCC of the Lung

- EGFR overexpression, gene amplification and aberrations of other ErbB receptors have all been implicated in the pathobiology of SqCC\(^1,2\)

- These findings likely account for the benefits these patients derive from erlotinib\(^{11-13}\) and other EGFR-directed therapies in different treatment settings,\(^{14-16}\) despite the low frequency of EGFR-activating mutations\(^{17}\)

<table>
<thead>
<tr>
<th>ErbB Receptor</th>
<th>Frequency (%)</th>
</tr>
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<tbody>
<tr>
<td>EGFR overexpression(^2-5)</td>
<td>26–86</td>
</tr>
<tr>
<td>EGFR amplification(^2,5)</td>
<td>15–27</td>
</tr>
<tr>
<td>EGFRvIII mutation(^6)</td>
<td>5</td>
</tr>
<tr>
<td>EGFR kinase domain mutation(^7)</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>ERBB2 mutation/amplification(^2)</td>
<td>5</td>
</tr>
<tr>
<td>ERBB3 mutation(^8)</td>
<td>1</td>
</tr>
<tr>
<td>ERBB3 overexpression(^9)</td>
<td>10</td>
</tr>
<tr>
<td>ERBB4(^10)</td>
<td>8</td>
</tr>
</tbody>
</table>

Amp = amplification; EGFR = epidermal growth factor receptor; FGFR = fibroblast growth factor receptor; SqCC = squamous cell carcinoma.

Afatinib is the First Irreversible ErbB Family Blocker

- Afatinib covalently binds and irreversibly blocks EGFR, HER2, and ErbB4
- Targeting the whole ErbB Family enhances the effect on important signaling pathways

**LUX-Lung 8: Study Design**

- Advanced SqCC NSCLC (Stage IIIB/IV)
- PD after ≥4 cycles of a first-line platinum doublet
- ECOG PS 0 or 1
- No prior anti-EGFR therapy
- No active brain metastases

Randomisation 1:1 (N=795)

- Afatinib (n=398)
  - 40 mg qd

- Erlotinib (n=397)
  - 150 mg qd

Treatment until disease progression or unacceptable AEs

- Stratification: East Asian vs non-East Asian
- Tumour tissue collected for correlative science
- Radiographic tumour assessment at baseline; Weeks 8, 12, 16; every 8 weeks thereafter
- Primary endpoint: PFS; key secondary endpoint: OS

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AE = adverse event; EGFR = epidermal growth factor receptor; ECOG PS = Eastern Cooperative Oncology Group performance status; NSCLC = non-small cell lung cancer; OS = overall survival; PD = disease progression; PFS = progression-free survival; qd = once daily; SqCC = squamous cell carcinoma.

LUX-Lung 8: Significant Improvement in PFS and OS With Afatinib Compared With Erlotinib

Updated PFS analysis by Independent Review (n=795)

- Afatinib: 40 mg QD (n=398)
- Erlotinib: 150 mg QD (n=397)

Patients progressed or died, n (%):
- Afatinib: 299 (75.1)
- Erlotinib: 306 (77.1)

Median PFS (months):
- Afatinib: 2.6
- Erlotinib: 1.9

HR 0.81; 95% CI: 0.69–0.98; \( P=0.0103 \)

Primary analysis of OS (key secondary endpoint) (n=795)

- Afatinib: 40 mg QD (n=398)
- Erlotinib: 150 mg QD (n=397)

Patients died, n (%):
- Afatinib: 307 (77.1)
- Erlotinib: 325 (81.9)

Median OS (months):
- Afatinib: 7.9
- Erlotinib: 8.8

HR 0.81; 95% CI: 0.69–0.95; \( P=0.0077 \)

Cl = confidence interval; HR = hazard ratio; OS = overall survival; PFS = progression-free survival; QD = once daily.

Post-hoc Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit

Post-hoc analysis identified 21 patients who received ≥12 months of afatinib treatment
- Median treatment duration was 17.6 months (range: 12.3–27.6 months)

Post-hoc Analysis of LUX-Lung 8 Patients Deriving Long-term Benefit

OS and PFS in Patients Deriving Long-term Benefit

• Median OS was 21.1 months (range: 12.9–31.6 months)

• Median PFS was 16.6 months (range: 2.8–25.8 months)

OS: Primary Analysis (ITT population)

Afatinib OS, 7.9 mo

Treatment Response* and OS in Patients Deriving Long-term Benefit

- Median OS was 21.1 months (range: 12.9–31.6 months)
- Median PFS (independent central review) was 16.6 months (range: 2.8–25.8 months)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Gemcitabine</td>
</tr>
<tr>
<td>5</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>10</td>
<td>Carboplatin/paclitaxel</td>
</tr>
<tr>
<td>15</td>
<td>Paclitaxel, gemcitabine</td>
</tr>
<tr>
<td>20</td>
<td>Docetaxel</td>
</tr>
<tr>
<td>25</td>
<td>Gemcitabine, carboplatin, paclitaxel/carboplatin</td>
</tr>
<tr>
<td>30</td>
<td>Paclitaxel, gemcitabine</td>
</tr>
<tr>
<td>35</td>
<td>Paclitaxel, gemcitabine</td>
</tr>
</tbody>
</table>

*Stable disease unless noted otherwise (patient 2 was classified as non-evaluable); †Patients were ordered and numbered by treatment duration, with patient 1 being on treatment longest; ‡First observed response at time of tumour measurement; §Last observed response at time of tumour measurement; ¶Treatment ongoing until death; ‖Received ≥1 line of chemotherapy after afatinib.

CR = complete response; PR = partial response.

Yang J et al. ELCC 2017. Poster #102P.
Genomic Aberrations in Patients Deriving Long-term Benefit

- ErbB family mutations were more frequent in LTRs than in the overall afatinib-treated population

**All afatinib-treated patients (n=132*)**

- ErbB WT, 81.1%
- ErbB2, 6.8%
- ErbB3, 4.6%
- ErbB4, 2.3%
- EGFR, 6.8%

**LTRs (n=10*)**

- ErbB WT, 50.0%
- ErbB2, 20.0%
- ErbB3, 0%
- ErbB4, 10.0%
- EGFR, 20.0%

*Next-generation sequencing was undertaken in 10/21 LTRs and 132/398 afatinib-treated patients overall; WT = wild-type.

Yang J et al. ELCC 2017. Poster #102P.
Experience With Afatinib for SqCC of the Lung: Case Report From LUX-Lung 8

Baseline characteristics
• 59-year-old white male
• ECOG PS: 1
• Stage IV
• Primary site: left upper lobe
• Number of metastases: 2; no brain metastases
• Smoking status: ex smoker (41 pack-years)

Treatments
• First-line: carboplatin/paclitaxel (Aug 2012 to Oct 2012; best response: CR); no maintenance therapy
• Second-line: afatinib within LUX-Lung 8
Experience With Afatinib for SqCC of the Lung: Case Report From LUX-Lung 8

Outcomes with second-line afatinib

- **Treatment duration:** 19.6 months (Mar 2013 to Nov 2014)
  - **Afatinib dosage:** 40 mg for 28 days; 50 mg for 18.7 months

- **PFS:** 17.1 months
- **OS:** 23.1 months

Biomarker analysis

- **Mutation:** *HER2* E395K
See You at the Poster!

- P3.01 – Advanced NSCLC (ID 621)
  09:30 am – 04:00 pm | 10/18/2017 | Location: Exhibit Hall (Hall B + C)
  Type: Poster Session with Presenters Present | Track: Advanced NSCLC

- P3.01-043 – Impact of ErbB Mutations on Clinical Outcomes in Afatinib- or Erlotinib-Treated Patients with SCC of the Lung
Summary and Conclusions

• LUX-Lung 8\textsuperscript{1}
  - Afatinib significantly improved PFS vs erlotinib: 2.6 vs 1.9 months (HR 0.81; \(P=0.0427\))
  - Afatinib significantly improved OS vs erlotinib: 7.9 vs 6.8 months (HR 0.81, \(P=0.0077\))

  - Survival rates at 12 and 18 months favored afatinib
    - 12 months (afatinib vs erlotinib): 36\% vs 28\% (\(P=0.016\))
    - 18 months: 22\% vs 14\% (\(P=0.013\))

  - In patients on afatinib for \(\geq\) 12 months, a median survival benefit of nearly 2 years was seen
    - ErbB family mutations were more frequent in this group\textsuperscript{3}

Summary and Conclusions

In treatment of SqCC, afatinib should be considered:

- As a treatment option in patients who have failed previous treatment with chemotherapy and immunotherapy
- In the second-line setting in patients who are not eligible for immune checkpoint inhibitors

HR = hazard ratio; OS = overall survival; PFS = progression-free survival; SqCC = squamous cell carcinoma.

Questions?