Common Options for Uncommon Mutations

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Disclosures

Has received honoraria for speeches or participated in compensated advisory boards for:

Boehringer Ingelheim, Eli Lilly, Bayer, Roche/Genentech/Chugai, Astellas, MSD, Merck Serono, Pfizer, Novartis, Celgene, Merrimack, Yuhan Pharmaceuticals, BMS, Ono Pharmaceutical, Daiichi Sankyo, AstraZeneca, Takeda, Hansoh Pharmaceutical, Blueprint Medicines, G1 Therapeutics
**EGFR Mutations in NSCLC**

The most frequent *EGFR* mutations in these populations are the common Del19 and/or L858R mutations1,2

- Exon 19 deletion (Del19) \(\approx 45\%-62\%\)1,2
- Exon 21 L858R \(\approx 33\%-40\%\)1,2

\(\approx 10\%-15\%\)
of tumours harbour uncommon *EGFR* mutations, comprising mutations in exons 18-212,3

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EGFR Mutations in NSCLC (cont’d)

- Uncommon mutations consist of:
  - Exon 20 insertions (9%)
  - Uncommon mutations with Del19 or L858R complex mutations (30%)
  - Uncommon mutations alone or in combination with other uncommon mutations (61%)

Exon 18 nonclassical, single (n=25), 3.0%
Exon 19 nonclassical, single (n=3), 0.4%
Exon 20 insertionsa (n=22), 3.0%
Exon 20 nonclassical, single (n=9), 1.0%
Exon 21 nonclassical, single (n=9), 1.0%
Nonclassical mutation with Del19 and L858R (n=48), 6.0%
Complex nonclassical without Del19 and L858R (n=14), 2.0%

*Exon 20 insertions (except A763_Y764 ins FQEA).
EGFR = epidermal growth factor receptor; NSCLC = non-small cell lung cancer.
In Vitro Activity of First-, Second-, and Third-Generation TKIs Against Uncommon EGFR Mutations

- Irreversible second- and third-generation TKIs overcome resistance induced by uncommon secondary mutations (L858R/L747S, L858R/D761Y, or L858R/T854A) in cell-based assays\(^1\)

- First- and third-generation TKIs demonstrated reduced activity in cell lines harbouring uncommon mutations (L858M/L681Q,\(^2\) L861Q,\(^3\) and S768I\(^3\)), whereas the afatinib response was similar across cell lines\(^2,3\)

- Afatinib had greater sensitivity to exon 18 mutations (G719A, E709K, and Del18) than first- and third-generation TKIs\(^4\)

\(\text{IC}_{50} = \text{half-maximal inhibitory concentration.}\)

First-Line Clinical Data: Prospective Efficacy Assessments in the LUX-Lung Programme

- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations\(^1-4\)
- 75 of 600 patients (12.5\%) given afatinib harboured uncommon EGFR mutations in a combined post-hoc analysis of LUX-Lung 2/3/6\(^4\)
  - 3 patients achieved CR; 1 each with G719X, K739_1744dup6, and L858R+E709G/V)

First-Line Clinical Data: Prospective Efficacy Assessments in the LUX-Lung Programme

LUX-Lung 2/3/6: Tumour Shrinkage by Independent Review (n=67\(^a\))\(^4\)

- **De novo T790M mutations (n=14):**

- **Point mutations or duplications in exons 18-21 (n=33):**

- **Exon 20 insertions (n=20)**

\(^a\) 8 patients were not included because of insufficient data.

**CR** = complete response.

Clinical Data: Response to Afatinib in NSCLC Harbouring Uncommon EGFR Mutations in LUX-Lung 2/3/6\textsuperscript{1,2}

Point Mutations or Duplications in Exons 18-21, alone or in combination with each other\textsuperscript{a} (n=38)

- **De novo T790M mutations in exon 20, alone or in combination with other mutations** (n=14):
  - ORR: 14%; mPFS: 2.9 (95% CI: 1.2-8.3) months; mOS: 14.9 (95% CI: 8.1-24.9); DCR: 64.3% (n=9)
- **Exon 20 insertions** (n=23):
  - ORR: 9%; mPFS: 2.7 (95% CI: 1.8-4.2) months; mOS: 9.2 (95% CI: 4.1-14.2); DCR: 65.2% (n=15)

\textsuperscript{a}Consists of patients with all point mutations or duplications in exons 18–21 (Leu861Gln, Gly719Ser, Gly719Ala, Gly719Cys, Ser768Ile, and rare others).

CI = confidence interval; DCR = disease control rate; mOS = median overall survival; mPFS = median progression-free survival; ORR = objective response rate; OS overall survival; PFS = progression-free survival.

\textsuperscript{1} Yang et al. Lancet Oncol. 2015;16:830; \textsuperscript{2} Arrieta et al. Presented at LALCA 2018. Abstract 93.
First-Line Real-World Data: Retrospective Analysis of PFS in 56 Patients Treated With Afatinib or First-Generation TKIs\textsuperscript{a}

• In all mutation groups analysed, the afatinib group exhibited longer mPFS compared with first-generation TKIs
  
  – Entire uncommon mutations cohort, except exon 20 insertions\textsuperscript{b}: 11.0 vs 3.6 mo
  
  – G719X, S768I, or L861Q: 18.3 vs 2.6 mo
  
  – Uncommon mutations with Del19 or L858R: 11.0 vs 8.2 mo
  
  – Uncommon mutation alone or in combination with other uncommon mutations: 18.3 vs 2.8 mo

\textsuperscript{a}Retrospective single-center, Chinese study of patients with stage IIIB-IV lung adenocarcinoma who underwent EGFR mutation testing from June 2011 to July 2016. 56 patients with non-classical mutations who received EGFR-TKI treatment and completed follow-up were included in the analysis.

\textsuperscript{b}Exon 20 insertions (except A763_Y764 insFQEA).
Prospective Real-World Data: Afatinib in EGFR TKI–naive Patients With Uncommon Mutations
Pooled Analysis From an Asian Phase 3b Study and a German Noninterventional Study

• In the combined analysis of subgroups with uncommon mutations (N=54), 5.6% of patients had an ECOG PS 2 at baseline

Best response to afatinib in EGFR mutation subgroups (by investigator review)

<table>
<thead>
<tr>
<th>Mutation Subgroup</th>
<th>ORR (%)</th>
<th>DCR (%)</th>
<th>CR (%)</th>
<th>PR (%)</th>
<th>SD (%)</th>
<th>PD (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L861Q, S768I, G719X (n=34)</td>
<td>58.8%</td>
<td>91.2%</td>
<td>5.9%</td>
<td>52.9%</td>
<td>32.4%</td>
<td>8.8%</td>
</tr>
<tr>
<td>L861Q (n=7)</td>
<td>57.1%</td>
<td>100.0%</td>
<td>57.1%</td>
<td>52.6%</td>
<td>31.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>G719X (n=19)</td>
<td>57.9%</td>
<td>89.5%</td>
<td>5.3%</td>
<td>52.6%</td>
<td>31.6%</td>
<td>10.5%</td>
</tr>
<tr>
<td>Compound Mutationsa (n=19)</td>
<td>47.4%</td>
<td>89.5%</td>
<td>47.4%</td>
<td>42.1%</td>
<td>31.6%</td>
<td>10.5%</td>
</tr>
</tbody>
</table>


ECOG = Eastern Cooperative Oncology Group; NIS = noninterventional study; CR = complete response; PD = progressive disease; PR = partial response; PS = performance status; SD = stable disease.
Prospective Real-World Data With Afatinib in EGFR TKI-naive Patients With Uncommon Mutations (cont’d): PFS

PFS in EGFR Mutation Subgroups

<table>
<thead>
<tr>
<th>EGFR mutation</th>
<th>Median PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>L861Q, S768I, G719X (n=40)</td>
<td>10.7</td>
</tr>
<tr>
<td>L861Q (n=9)</td>
<td>10.7</td>
</tr>
<tr>
<td>G719X (n=14)</td>
<td>10.6</td>
</tr>
<tr>
<td>Compound mutations (n=20)</td>
<td>7.3</td>
</tr>
</tbody>
</table>


KCSG-LU15-09: Phase 2 Trial of Osimertinib in Patients With Uncommon EGFR m+ NSCLC

- All patients included in this analysis (N=36) had an ECOG PS 0-1 at baseline

Osimertinib in Uncommon EGFR m+ NSCLC

- The most common AEs (≥15%, all grade) were rash, anorexia, and diarrhea

**ORR by Mutation Type**
- S768I (n=8): 37.5%
- G719X (n=19): 52.6%
- L861Q (n=9): 77.8%

<table>
<thead>
<tr>
<th>Mutation Type</th>
<th>ORR (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>S768I</td>
<td>37.5%</td>
</tr>
<tr>
<td>G719X</td>
<td>52.6%</td>
</tr>
<tr>
<td>L861Q</td>
<td>77.8%</td>
</tr>
</tbody>
</table>

**Median PFS (range), months**
- 9.5 (1.0-20.1)

**Median DoR (95% CI), months**
- 7.0 (4.7-9.3)

- All patients included in this analysis (N=36) had an ECOG PS 0-1 at baseline

Data cutoff November 2017.

- Uncommon mutation categories overlap for those with compound mutations, so individual patients might appear in more than one category.

AE = adverse event; DoR = duration of response; EGFR m+ = epidermal growth factor receptor mutation-positive.

Ongoing Investigations of Antitumor Activity in Patients With EGFR Exon 20 Mutant NSCLC

- Poziotinib in Exon 20 mutant EGFR m+ NSCLC (n=44) - Phase 2\(^1\)
  - ORR (best response): 55%
  - ORR (confirmed): 43%

- TAK-788 in Exon 20 insertion EGFR m+ NSCLC (n=28) - Phase 1/2\(^2\)
  - ORR: 43%
  - DCR: 86%

- JNJ-372, an EGFR-cMet bispecific ab, in Exon 20 insertion EGFR m+ NSCLC (n=27) - Phase 1\(^3\)
  - 8/27 (30%) patients with best response of PR (6 confirmed)

Ab = antibody.

Summary

- The LUX-Lung programme provides the largest series of prospective efficacy data in uncommon mutations\(^1-4\)
- Afatinib had clinically meaningful activity in NSCLC tumours harbouring point mutations or duplications in exons 18-21 (eg, G719X, S768I, L861Q K739_1744dup6, and L858R+E709G/V)\(^4\)
- Data from real-world studies with afatinib are in line with analyses from the LUX-Lung trials\(^5,6\)
- Limited data (n=36) with osimertinib from a Korean phase 2 study show activity in the major uncommon mutations\(^7\)
- Emerging studies highlight new compounds targeting EGFR exon 20 insertions (poziotinib, TAK-788, JNJ-372)\(^8-10\)
- Taken together, we are making progress in the use of targeted therapy for the treatment of NSCLC with uncommon EGFR mutations

CUP = compassionate use programme; EAP = expanded-access programme.