Neratinib in pretreated *EGFR* exon 18-mutant non-small cell lung cancer (NSCLC): initial findings from the SUMMIT basket trial

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*EGFR* exon 18 mutations represent 5% of all *EGFR* mutations detected in lung cancer.

**EGFR mutations associated with drug resistance:**
- L747S
- D761Y
- T854A
- E884K

**EGFR mutations associated with drug sensitivity:**
- V765A
- T783A
- L858R
- G719C
- G719S
- G719A
- V689M
- N700D
- E709K/Q
- S720P
- ΔE746-A750
- ΔE746-T751
- ΔE746-A750 (ins RP)
- ΔE746-T751 (ins A/I)
- ΔE746-T751 (ins VA)
- ΔE746-S752 (ins A/V)
- ΔL747-E749 (A750P)
- ΔL747-A750 (ins P)
- ΔL747-T751
- ΔL747-T751 (ins P/S)
- ΔL747-S752
- ΔL747-T752 (E746V)
- ΔL747-T752 (P753S)
- ΔL747-S752 (ins Q)
- ΔL747-P753
- ΔL747-P753 (ins S)
- ΔS752-I759

**EGFR exon 18 mutations are highly sensitive to neratinib in vitro**

Neratinib: oral, irreversible, tyrosine kinase inhibitor of EGFR (ERBB1), HER2 (ERBB2), & HER4 (ERBB4)*

Comparative TKI effects in *EGFR* exon 18 (G719A) mutation-positive Ba/F3 cells#

Western blot analyses of transfected HEK293 cells#

- The phosphorylation of EGFR was almost inhibited by **100 nmol/L afatinib** in Del18, E709K, G719A, and Del19 cells.
- **10 nmol/L neratinib** more effectively inhibited the phosphorylation of EGFR in G719A cells.

Prior phase 2 trial of neratinib in EGFR TKI-refractory NSCLC

4/167 (2%) pts had EGFR exon 18 mutations (G719X)
- 1 patient did not have measurable disease by central review

All patients with G719 mutations (n=4) had clinical benefit
- 3 PRs
- 1 SD lasting >40 weeks
- Median PFS 52.7 weeks (90% CI 25.6–57.0 weeks)


EGFR exon 18 mutations are highly sensitive to neratinib: a POC trial
SUMMIT study design for EGFR exon 18-mutant lung cancer cohort

**EGFR exon 18-mutant Lung Cancer**

**Open-label, single-arm cohort**

**Neratinib monotherapy**

(240 mg, oral daily)

Mandatory Loperamide prophylaxis: oral 4 mg TID days 1–14, 4 mg BID days 15–46; as needed PRN

**Primary endpoint**

- Objective response rate at first post-baseline tumor assessment (Week 8) (ORRWk8)

**Secondary endpoints**

- ORR (confirmed by RECIST criteria)
- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Progression-free survival (PFS)
- Safety
- Biomarkers

**Simon 2-stage design**

- If ≥1 response in first evaluable 7 patients, expand cohort to Stage 2 (N=18)
- If ≥4 responses in Stage 2, expand or breakout

**Tumor assessments**

- RECIST v1.1 (primary criteria)
- PET response criteria (RECIST non-evaluable)

**Statistical methods**

- ORR_{first}, ORR, CBR: associated 95% CI
- Median PFS: Kaplan-Meier estimate with 95% CI
- DOR

**Key inclusion criteria**

- Histologically confirmed lung cancers for which no curative therapy exists
- Documented EGFR exon 18 mutation by local method (any CAP/CLIA-certified lab)
- Prior treatment with EGFR or pan-HER TKI allowed (afatinib, dacomitinib, osimertinib, etc)
- ECOG status of 0 to 2
- RECIST 1.1 disease only

**Key exclusion criteria**

- Patients who are receiving any other anticancer agents
- Symptomatic or unstable brain metastases
- Women who are pregnant or breast-feeding
- Known KRAS activating co-mutation

ClinicalTrials.gov Identifier: NCT01953926
## EGFR exon 18-mutant lung cancer cohort: baseline characteristics

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Safety/efficacy evaluable patients (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age, years (range)</strong></td>
<td>67 (56–83)</td>
</tr>
<tr>
<td>&lt;65 years, n (%)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>≥65 years, n (%)</td>
<td>7 (64)</td>
</tr>
<tr>
<td><strong>Gender, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>5 (45)</td>
</tr>
<tr>
<td>Male</td>
<td>6 (55)</td>
</tr>
<tr>
<td><strong>ECOG performance status, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>5 (45)</td>
</tr>
<tr>
<td>1</td>
<td>6 (55)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (9)</td>
</tr>
<tr>
<td>White</td>
<td>10 (91)</td>
</tr>
<tr>
<td><strong>Median number of prior therapies in metastatic/locally advanced setting (range)</strong></td>
<td>2 (1–3)</td>
</tr>
<tr>
<td>Prior checkpoint inhibitor, n (%)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Prior chemotherapy, n (%)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Prior EGFR tyrosine kinase inhibitor, n (%)</td>
<td>10 (91)</td>
</tr>
<tr>
<td>Gefitinib/erlotinib</td>
<td>7 (58)</td>
</tr>
<tr>
<td>Osimertinib</td>
<td>3 (25)</td>
</tr>
<tr>
<td>Afatinib</td>
<td>2 (17)</td>
</tr>
</tbody>
</table>

Data cut-off: 21-Aug-2020
## EGFR exon 18-mutant lung cancer cohort: Efficacy summary

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Efficacy evaluable patients (n=11)</th>
<th>TKI pre-treated subgroup (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objective response (confirmed), a,n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ORR,a† % (95% CI)</td>
<td>36 (11–69)</td>
<td>40 (12–74)</td>
</tr>
<tr>
<td><strong>Best overall response, n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Best overall response rate, % (95% CI)</td>
<td>54 (23–83)</td>
<td>60 (26–88)</td>
</tr>
<tr>
<td><strong>Median DOR,b months (95% CI)</strong></td>
<td>7.5 (4.0–NE)</td>
<td>7.5 (4.0–NE)</td>
</tr>
<tr>
<td></td>
<td>(1.9*, 4.0, 7.5, 9.2*)</td>
<td>(1.9*, 4.0, 7.5, 9.2*)</td>
</tr>
<tr>
<td><strong>Clinical benefit,c,n</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR or PR</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>SD ≥16 weeks</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Clinical benefit rate, % (95% CI)</td>
<td>73 (39–94)</td>
<td>80 (44–97)</td>
</tr>
<tr>
<td><strong>Median PFSb time to event, months (95% CI)</strong></td>
<td>6.9 (2.1–NA)</td>
<td>9.1 (3.7–NA)</td>
</tr>
</tbody>
</table>

*aORR (objective response rate) defined as either a CR or PR that is confirmed no less than 4 weeks after the criteria for response are initially met; bKaplan-Meier analysis in safety population; cCBR (clinical benefit rate) defined as confirmed CR or PR or SD for ≥16 weeks (within +/- 7-day visit window); †Data for ORR at week 8 (ORR8,w) and ORR (RECIST 1.1 confirmed) are identical and are only presented once. DOR, duration of response; PFS, progression-free survival; *response ongoing
EGFR exon 18-mutant lung cancer cohort:
Treatment duration, best response and best change in tumor size

Mutation category
- G719X
- G719X + E709X
- G719X + S768I
- G719C; S768I; T790M
- E709_T710delinsD; EGFRamp

Best response (RECIST v1.1)
- Partial response (RECIST)
- Stable disease (RECIST)
- Disease progression (RECIST)
- Progressive disease (RECIST)

Duration of treatment
- G719A
- G719X
- G719C; E709K
- G719X
- G719X; S768I
- G719C; S768I; T790M
- G719X; S768I
- G719A; E709A
- G719X; S768I; T790M
- G719C; S768I
- E709_T710delinsD; EGFRamp

Data cut-off: 21-Aug-2020
EGFR exon 18-mutant lung cancer cohort: Most common treatment-emergent adverse events >10%

<table>
<thead>
<tr>
<th>TEAE, n (%)</th>
<th>Safety evaluable patients (n=11)</th>
<th>Any grade</th>
<th>Grade ≥3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>5 (45.5)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (36.4)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (27.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (27.3)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>3 (27.3)</td>
<td>1 (9.1)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (18.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>2 (18.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>2 (18.2)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (18.2)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Key safety findings
- Well tolerated with mandatory loperamide prophylaxis (first 2 cycles)
- 4 patients (36%) reported grade 1 and 1 patient (9%) reported grade 2 diarrhea
- No evidence of grade 3 diarrhea, ILD, or skin rashes
- No patients required a dose hold, dose reduction, hospitalization or permanently discontinued neratinib due to diarrhea

Data cut-off: 21-Aug-2020
Female, 61 years, former smoker

Dec 2016: stage IV lung adenocarcinoma with lung, lymph nodes, bone and brain metastasis and EGFR (G719X) mutation

Dec 2016: SBRT on brain; 1st-line erlotinib achieving SD as best response and clinical benefit

Nov 2018: asymptomatic brain/lung progression; 2nd-line neratinib (duration of treatment 46.3 weeks)

Jan 2019: PR (60% reduction in tumor burden by RECIST 1.1) and stable brain mets on neratinib

Sep 2019: lung PD; 3rd-line osimertinib
Summary/conclusions

- Single-arm phase 2 trial showing early clinical efficacy of single-agent neratinib in TKI-refractory EGFR exon 18-mutant NSCLC
  - Confirmed ORR: 40% & Stable disease (≥ 16 weeks): 40%
  - CBR: 80%
  - DOR: 7.5 months
  - Median PFS: 9.1 months
- Well-tolerated with no evidence of grade 3 diarrhea with mandatory loperamide prophylaxis
- No reported cases of ILD and skin rashes
- Enrollment is ongoing

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