Behandelsequentie patiënten met drivermutaties

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Disclosures

I attended advisory boards and/or provided lectures for: Roche, Eli Lilly, Boehringer Ingelheim, Astra Zeneca, Pfizer, BMS, Amgen, Novartis, MSD; for which my institute received honoraria.

This study was supported by grants of the Dutch Cancer Society and European Respiratory Society.
Oncogene drivers in adenocarcinoma

Key
1 - Phase I  3 - Phase III
2 - Phase II  4 - Approved

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 309

MEK1
- Trametinib
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PIK3CA
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- PQR 309

-- 2016
Superior outcome with osimertinib in T790M+ NCLC

Mok, NEJM 2017
FLAURA: first line osimertinib vs SOC

Patients with locally advanced or metastatic NSCLC

Key inclusion criteria
- >18 years
- WHO performance status 0 / 1
- Exon 19 deletion / L858R (enrolment by local# or central† EGFR testing)
- No prior systemic anti-cancer / EGFR-TKI therapy
- Stable CNS metastases allowed

Stratification by mutation status (Exon 19 deletion / L858R) and race (Asian / non-Asian)

Osimertinib (80 mg p.o. qd) (n=279)

Randomised 1:1

RECIST 1.1 assessment every 6 weeks until objective progressive disease

EGFR-TKI SoC§:
- Gefitinib (250 mg p.o. qd) or Erlotinib (150 mg p.o. qd) (n=277)

Endpoints
- Primary endpoint: PFS based on investigator assessment (according to RECIST 1.1)
  - The study had a 90% power to detect a hazard ratio of 0.71 (representing an improvement in median PFS from 10 months to 14.1 months) at a two-sided alpha-level of 5%
- Secondary endpoints: objective response rate, duration of response, disease control rate, depth of response, overall survival, patient reported outcomes, safety

Crossover was allowed for patients in the SoC arm, who could receive open-label osimertinib upon central confirmation of progression and T790M positivity

### FLAURA: first line osimertinib vs SOC

**BASELINE CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic, %</th>
<th>Osimertinib (n=279)</th>
<th>SoC* (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex: male / female</td>
<td>36 / 64</td>
<td>38 / 62</td>
</tr>
<tr>
<td>Age, median (range), years</td>
<td>64 (26–85)</td>
<td>64 (35–93)</td>
</tr>
<tr>
<td>Race: White / Asian / other§</td>
<td>36 / 62 / 1</td>
<td>36 / 62 / 1</td>
</tr>
<tr>
<td>Smoking status: never / ever</td>
<td>65 / 35</td>
<td>63 / 37</td>
</tr>
<tr>
<td>CNS metastases at study entry‡</td>
<td>19</td>
<td>23</td>
</tr>
<tr>
<td>WHO performance status§: 0 / 1</td>
<td>40 / 60</td>
<td>42 / 58</td>
</tr>
<tr>
<td>Overall disease classification¶: metastatic / advanced</td>
<td>95 / 5</td>
<td>95 / 5</td>
</tr>
<tr>
<td>Histology: adenocarcinoma / other</td>
<td>99 / 1</td>
<td>98 / 2</td>
</tr>
<tr>
<td>EGFR mutation at randomisation**: Exon 19 deletion / L858R</td>
<td>63 / 37</td>
<td>63 / 37</td>
</tr>
</tbody>
</table>
FLAURA: first line osimertinib vs SOC

PRIMARY ENDPOINT: PFS BY INVESTIGATOR ASSESSMENT

342 events in 556 patients at DCO: 62% maturity; osimertinib: 136 events (49%), SoC: 206 events (74%)

Median PFS, months (95% CI)
- Osimertinib: 18.9 (15.2, 21.4)
- SoC: 10.2 (9.6, 11.1)

HR 0.46
(95% CI 0.37, 0.57)
p < 0.0001
FLAURA: first line osimertinib vs SOC

**PFS* ACROSS SUBGROUPS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Favours osimertinib</th>
<th>Favours SoC</th>
<th>Hazard ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (n=556)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log Rank (primary)</td>
<td></td>
<td></td>
<td>0.46 (0.37, 0.57)</td>
</tr>
<tr>
<td>Cox PH</td>
<td></td>
<td></td>
<td>0.46 (0.37, 0.57)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (n=206)</td>
<td></td>
<td></td>
<td>0.58 (0.41, 0.82)</td>
</tr>
<tr>
<td>Female (n=350)</td>
<td></td>
<td></td>
<td>0.40 (0.30, 0.52)</td>
</tr>
<tr>
<td>Age at screening</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;65 (n=298)</td>
<td></td>
<td></td>
<td>0.44 (0.33, 0.58)</td>
</tr>
<tr>
<td>≥65 (n=258)</td>
<td></td>
<td></td>
<td>0.49 (0.35, 0.67)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (n=347)</td>
<td></td>
<td></td>
<td>0.55 (0.42, 0.72)</td>
</tr>
<tr>
<td>Non-Asian (n=209)</td>
<td></td>
<td></td>
<td>0.34 (0.23, 0.48)</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=199)</td>
<td></td>
<td></td>
<td>0.48 (0.34, 0.68)</td>
</tr>
<tr>
<td>No (n=357)</td>
<td></td>
<td></td>
<td>0.45 (0.34, 0.59)</td>
</tr>
<tr>
<td>CNS metastases</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n=116)</td>
<td></td>
<td></td>
<td>0.47 (0.30, 0.74)</td>
</tr>
<tr>
<td>No (n=449)</td>
<td></td>
<td></td>
<td>0.46 (0.36, 0.59)</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (n=228)</td>
<td></td>
<td></td>
<td>0.39 (0.27, 0.56)</td>
</tr>
<tr>
<td>1 (n=327)</td>
<td></td>
<td></td>
<td>0.50 (0.36, 0.66)</td>
</tr>
<tr>
<td>EGFR mutation at randomisation²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exon 19 deletion (n=349)</td>
<td></td>
<td></td>
<td>0.43 (0.32, 0.56)</td>
</tr>
<tr>
<td>L858R (n=207)</td>
<td></td>
<td></td>
<td>0.51 (0.36, 0.71)</td>
</tr>
<tr>
<td>EGFR mutation by ctDNA³</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n=359)</td>
<td></td>
<td></td>
<td>0.44 (0.34, 0.57)</td>
</tr>
<tr>
<td>Negative (n=124)</td>
<td></td>
<td></td>
<td>0.48 (0.28, 0.80)</td>
</tr>
<tr>
<td>Centrally confirmed EGFR mutation⁴</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive (n=500)</td>
<td></td>
<td></td>
<td>0.43 (0.34, 0.54)</td>
</tr>
<tr>
<td>Negative (n=9)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*PFS: progression-free survival
FLAURA: first line osimertinib vs SOC

PFS* IN PATIENTS WITH AND WITHOUT CNS METASTASES AT STUDY ENTRY

With CNS metastases (n=116)

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib: 15.2 (12.1, 24.4)</td>
</tr>
<tr>
<td>SoC: 9.6 (7.0, 12.4)</td>
</tr>
</tbody>
</table>

HR 0.47
(95% CI 0.30, 0.74)
p=0.0009

Without CNS metastases (n=440)

<table>
<thead>
<tr>
<th>Median PFS, months (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osimertinib: 18.1 (15.2, 23.5)</td>
</tr>
<tr>
<td>SoC: 10.9 (9.6, 12.3)</td>
</tr>
</tbody>
</table>

HR 0.46
(95% CI 0.36, 0.59)
p<0.0001

CNS progression events occurred in 17 (6%) vs 42 (15%) patients receiving osimertinib vs SoC (all patients)

FLAURA data cut-off: 12 June 2017

Maastricht UMC+
**FLAURA: first line osimertinib vs SOC**

**ALL CAUSALITY ADVERSE EVENTS* (≥15% OF PATIENTS)**

Median duration of exposure: osimertinib: 16.2 months (range 0.1 to 27.4), SoC: 11.5 months (range 0 to 26.2)

<table>
<thead>
<tr>
<th>AEs by preferred term, n (%)</th>
<th>Osimertinib (n=279)</th>
<th>SoC (n=277)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 1</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>161 (58)</td>
<td>120 (43)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>88 (32)</td>
<td>76 (27)</td>
</tr>
<tr>
<td>Paronychia</td>
<td>81 (29)</td>
<td>37 (13)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>80 (29)</td>
<td>65 (23)</td>
</tr>
<tr>
<td>Dermatitis acriform</td>
<td>71 (25)</td>
<td>61 (22)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>56 (20)</td>
<td>27 (10)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>48 (17)</td>
<td>40 (14)</td>
</tr>
<tr>
<td>Cough</td>
<td>46 (16)</td>
<td>34 (12)</td>
</tr>
<tr>
<td>Constipation</td>
<td>42 (15)</td>
<td>33 (12)</td>
</tr>
<tr>
<td>AST increased</td>
<td>26 (9)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>ALT increased</td>
<td>18 (6)</td>
<td>11 (4)</td>
</tr>
</tbody>
</table>
FLAURA: first line osimertinib vs SOC

- Klinisch relevante verlenging van progressievrije overleving
  - Ook bij hersenmetastasen

- Minder bijwerkingen

- Overleving nog niet te analyseren

- Osimertinib is nieuwe SOC voor EGFR mut positieve patienten (?)
• NSCLC with *BRAF* V600E mutations has histological features suggestive of an aggressive tumour\(^3\)
• Patients with *BRAF* V600E–mutant NSCLC demonstrated less-favorable outcomes with platinum-based chemotherapy\(^3,4\)

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BRF113928: Study design

Cohort A (monotherapy) planned n = 60

- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - ≥ 1 platinum-based chemotherapy

- Dabrafenib 150 mg BID

Interim futility analysis

Stage 1
n = 20

Stage 2
n = 20

Expansion
n= 20

Cohort B (combination D + T) planned n = 40

- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - 1-3 prior treatments
  - (≥ 1 platinum-based chemotherapy)

- Dabrafenib 150 mg BID
  - Trametinib 2 mg QD

Stage 1
n = 20

Stage 2
n = 20

Expansion
n= 20

Interim futility analysis

n = 57
(second to fourth line)

Cohort C (combination D + T first line) planned n = 25

- Stage IV NSCLC
  - BRAF V600E
  - ECOG PS 0-2
  - No prior treatment

- Dabrafenib 150 mg BID
  - Trametinib 2 mg QD

n = 25

Primary endpoint for each cohort:

ORR

## Patient Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Dabrafenib Plus Trametinib (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median age (range), years</strong></td>
<td>67 (44–91)</td>
</tr>
<tr>
<td><strong>Male sex, n (%)</strong></td>
<td>14 (39)</td>
</tr>
<tr>
<td><strong>Race, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>30 (83)</td>
</tr>
<tr>
<td>Asian</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Othera</td>
<td>3 (8)</td>
</tr>
<tr>
<td><strong>ECOG performance status ≤ 1, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>13 (36)</td>
</tr>
<tr>
<td>1</td>
<td>22 (61)</td>
</tr>
<tr>
<td>2</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Histology at initial diagnosis, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Nonsquamousb</td>
<td>35 (97)</td>
</tr>
<tr>
<td>Squamousc</td>
<td>1 (3)</td>
</tr>
<tr>
<td><strong>Smoking history, n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>10 (28)</td>
</tr>
<tr>
<td>Former</td>
<td>21 (58)</td>
</tr>
<tr>
<td>Current</td>
<td>5 (14)</td>
</tr>
</tbody>
</table>

*a Includes one patient each of Native American or other Pacific Islander, black or African American, and missing race.

*b Includes n = 32 patients with adenocarcinoma; and one patient each with adenosquamous carcinoma (predominantly adenocarcinoma), large cell carcinoma, and NSCLC not otherwise specified.

*c Patient had adenosquamous carcinoma (predominantly squamous cell carcinoma) histology.
Investigator-assessed Maximum change in target lesion by best response

Overall response rate, 64% (95% CI, 46–79)

Grey line at −30 represents the threshold for partial response, per Response Evaluation Criteria in Solid Tumors v1.1 criteria.
Numerical differences in median PFS between investigator and IRC assessments were primarily driven by censored observations for IRC (five patients who were assessed by the investigators as having PD had values for PFS close to the medians). Because no further tumour assessment scans were collected for these patients, and because the IRC did not assess these last scans as PD, the events for these patients in IRC assessment were based on the receipt of subsequent anticancer therapy.
### Most common aes (≥ 20%)

<table>
<thead>
<tr>
<th>Category</th>
<th>AEs, n (%)</th>
<th>All Grades</th>
<th>Grade 3/4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>General</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23 (64)</td>
<td>4 (11)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>13 (36)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Peripheral Oedema</td>
<td>13 (36)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>9 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Skin</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dry skin</td>
<td>12 (33)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>8 (22)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>20 (56)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Diarrhoea^</td>
<td>14 (39)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>12 (33)</td>
<td>3 (8)</td>
<td></td>
</tr>
<tr>
<td><strong>Nervous system</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>9 (25)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>8 (22)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Respiratory</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough</td>
<td>8 (22)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>12 (33)</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

^ One patient with diarrhoea had an event of an unknown grade.
Conclusions

- The ORR, DOR, and PFS observed in treatment naive patients in this cohort were similar to those reported for the previously-treated cohort.

<table>
<thead>
<tr>
<th></th>
<th>Previously Treated</th>
<th>Treatment Naive</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dabrafenib Monotherapy(^1,2) (n = 78)</td>
<td>Dabrafenib Plus Trametinib(^2) (n = 57)</td>
</tr>
<tr>
<td><strong>ORR (95% CI), %</strong></td>
<td>33 (23–45)</td>
<td>67 (53–79)</td>
</tr>
<tr>
<td><strong>DOR, median (95% CI), months</strong></td>
<td>9.6 (5.4–15.2)</td>
<td>9.8 (6.9–16.0)</td>
</tr>
<tr>
<td><strong>PFS, median (95% CI), months</strong></td>
<td>5.5 (3.4–7.3)</td>
<td>10.2 (6.9–16.7)</td>
</tr>
<tr>
<td><strong>OS, median (95% CI), months</strong></td>
<td>12.7 (7.3–16.3)</td>
<td>18.2 (14.3–NE)</td>
</tr>
</tbody>
</table>

use in patients with \(BRADF V600E\)–mutant metastatic NSCLC regardless of prior treatment history.
Oncogene drivers in adenocarcinoma

- EGFR Sensitizing: Gefitinib, Erlotinib, Matinib, Lemoitirib, Necitumumab, Rositinib
- ALK: Crizotinib
- MET: Crizotinib, Cabozantinib
- HER2: Trastuzumab, Emtansine, Afatinib
- ROS1: Crizotinib
- BRAF: Vemurafenib, Dabrafenib
- RET: Cabozantinib, Alectinib, Apatinib, Vandetanib, Ponatinib, Lenvatinib
- NTRK: Entrectinib, LOXO-101
- MEK1: Trametinib, Selumetinib, Cobimetinib
- PIK3CA: LY3023414, PQR 309
- KRAS: 25%
- EGFR: 17%
- Unknown Oncogenic Driver: 31%
Alectinib Stopped Growth Of Lung Longer Than Crizotinib, Study Indicated.

*Newsweek* (6/5, Wapner, 862K) reports that researchers found “in a Phase III clinical trial,” a new medication
The primary endpoint of the study was met: HR 0.47 (95% CI 0.34–0.65) P<0.001

Median PFS with alectinib was not reached compared with 11.1 months with crizotinib
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Patients with CNS mets at BL (by IRC)</th>
<th>ITT population (n=303)</th>
<th>Crizotinib (n=58)</th>
<th>Alectinib (n=64)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with measurable CNS disease (%)</td>
<td></td>
<td>22 (38)</td>
<td>21 (33)</td>
</tr>
<tr>
<td>CNS metastases treatment (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td></td>
<td>36 (62)</td>
<td>37 (58)</td>
</tr>
<tr>
<td>Whole brain RT</td>
<td></td>
<td>16 (28)</td>
<td>17 (27)</td>
</tr>
<tr>
<td>Radiosurgery</td>
<td></td>
<td>4 (7)</td>
<td>5 (8)</td>
</tr>
<tr>
<td>Other*</td>
<td></td>
<td>1 (2)</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Brain surgery</td>
<td></td>
<td>1 (2)</td>
<td>1 (2)</td>
</tr>
</tbody>
</table>

*1 patient in the alectinib arm received both radiosurgery and whole brain radiotherapy; 1 patient in the crizotinib arm and 3 patients in the alectinib arm had brain surgery combined with radiotherapy.

IRC = independent review committee; ITT = intent to treat; RT = radiotherapy
PFS BY CNS METASTASES STATUS AT BASELINE*

**Patients with CNS metastases at baseline†**

- Crizotinib (N=58)
- Alectinib (N=64)

![Graph showing PFS by CNS metastases status at baseline for Crizotinib and Alectinib.](#)

**Patients without CNS metastases at baseline**

- Crizotinib (N=93)
- Alectinib (N=88)

![Graph showing PFS by CNS metastases status at baseline for Crizotinib and Alectinib.](#)

*Investigator-assessed; †All patients with CNS metastases at baseline, irrespective of radiotherapy

NR = not reached

Shaw, et al. ASCO 2017
**PFS BY PRIOR RT IN PATIENTS WITH CNS METASTASES AT BASELINE**

Patients who had received prior RT

- **Crizotinib** (N=21)
- **Alectinib** (N=25)

**HR 0.34** (95% CI 0.15–0.78)
**P=0.0078**

**12.7 mo** (7.2–14.6)

Patients who had not received prior RT

- **Crizotinib** (N=37)
- **Alectinib** (N=39)

**HR 0.44** (95% CI 0.25–0.78)
**P=0.0041**

**7.2 mo** (3.9–8.6)

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*IRC, patients with brain metastases at baseline; §One patient in the alectinib arm with no CNS metastases by IRC had received prior RT, but was excluded here

RT= radiotherapy (includes both stereotactic radiosurgery and whole-brain radiotherapy)
CUMULATIVE INCIDENCE RATE OF CNS PROGRESSION (IRC, ITT)

For each patient, the first event of CNS progression, non-CNS progression or death was counted.

CIR = cumulative incidence rate

**Crizotinib**
- 12 month CIR: 58.3% (95% CI, 43.4–70.5)
- Patients WITH CNS metastases at baseline
  - 12 month CIR: 31.5% (95% CI, 22.1–41.3)
- Patients WITHOUT CNS metastases at baseline
  - 12 month CIR: 16.0% (95% CI, 8.2–26.2)

**Alectinib**
- 12 month CIR: 4.6% (95% CI, 1.5–10.6)
- Patients WITH CNS metastases at baseline
  - 12 month CIR: 10.0% (95% CI, 8.2–10.6)
- Patients WITHOUT CNS metastases at baseline
  - 12 month CIR: 4.6% (95% CI, 1.5–10.6)

Alectinib delayed CNS progression in patients with and without CNS metastases at baseline compared with crizotinib.

Oncogene drivers in adenocarcinoma

Key
1 - Phase I  3 - Phase III
2 - Phase II  4 - Approved

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 399

NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib

RET
- Cabozantinib
- Alectinib
- Apatinib
- Vemurafenib
- Ponatinib
- Lenvatinib

BRAF
- Vemurafenib
- Dabrafenib

KRAS
25%

EGFR Sensitizing
17%

ALK
7%

MET
3%

ROS1
2%

HER2
2%

Unknown Oncogenic Driver Detected
31%

Molecular Targets in Adenocarcinoma

EGFR Sensitizing
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Nedtumumab
- Rociletinib

ALK
- Crizotinib
- Alectinib
- Ceritinib
- Lorlatinib
- Brigatinib

MET
- Crizotinib
- Cabozantinib

HER2
- Trastuzumab emtansine
- Afatinib
- Dacomitinib

ROS1
- Crizotinib
- Cabozantinib
- Ceritinib
- Lorlatinib
- DS-6051b

BRAF
- Vemurafenib
- Dabrafenib

RET
- Cabozantinib
- Alectinib
- Apatinib
- Vemurafenib
- Ponatinib
- Lenvatinib

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NTRK1
- Entrectinib
- LOXO-101
- Cabozantinib
- DS-6051b

Maastricht UM
Tsao, JTO 2016
1308PD: Preliminary efficacy and safety of lorlatinib in pts (Pts) with ROS1-positive non-small cell lung cancer (NSCLC) – Besse B, et al

• Study objective
  – To evaluate the efficacy and safety of lorlatinib in patients with ROS1-positive NSCLC

Key patient inclusion criteria

• Locally advanced/metastatic NSCLC with ROS1 mutation
• With or without asymptomatic untreated or treated CNS metastases
• No restriction on previous therapy (n=47)

Primary endpoints

  ORR (RECIST v1.1), intracranial ORR

Secondary endpoints

  DoR, PFS, safety

Lorlatinib 100 mg/day in 21-day cycles

*Treatment was permitted to continue after PD if the patient was still experiencing clinical benefit

1308PD: Preliminary efficacy and safety of lorlatinib in pts (Pts) with ROS1-positive non-small cell lung cancer (NSCLC) – Besse B, et al

- Key results

Best change in tumour size from baseline: overall

- No prior crizotinib
- Prior crizotinib ± chemotherapy
- Prior crizotinib + ceritinib

* Off treatment or PD occurred
1308PD: Preliminary efficacy and safety of lorlatinib in pts (Pts) with ROS1-positive non-small cell lung cancer (NSCLC) – Besse B, et al

- **Key results (cont.)**
  - 53% of included patients had CNS metastases, and 66% had received prior crizotinib
  - Response
    - ORR in ROS1-positive patients was 36.2% (95%CI 22.7, 51.5); 22/47(46.8%) had best response of SD
    - Intracranial ORR was 56.0% (95%CI 30.2, 59.9), 9 patients had CR
    - Median DoR was 9.9 months (95%CI 6.9, 12.5)
  - Safety
    - Most TRAEs were grade 1 or 2; there were no grade 4–5 events
    - The most common TRAEs were hypercholesterolaemia (83%) and hypertriglyceridaemia (55%)

- **Conclusions**
  - Lorlatinib demonstrated clinical activity in patients with ROS1-positive NSCLC, including those with CNS involvement and those who had received prior crizotinib therapy
  - Treatment was generally well tolerated, with the most common TRAE being lipid elevations that were managed with lipid-lowering medication
Entrectinib
CNS-Active, Potent and Selective ROS1 and TRK Inhibitor

- 30x more potent than crizotinib against ROS1
- Most potent pan-TRK inhibitor in clinical development; demonstrated clinical activity in multiple tumor histologies
- Designed to cross the blood-brain barrier, with demonstrated clinical activity in primary brain tumors and secondary CNS metastases

<table>
<thead>
<tr>
<th>Target</th>
<th>ROS1</th>
<th>TRKA</th>
<th>TRKB</th>
<th>TRKC</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC$_{50}$ (nM)$^a$</td>
<td>0.2</td>
<td>1.7</td>
<td>0.1</td>
<td>0.1</td>
</tr>
</tbody>
</table>

$^a$ Based on biochemical assay
Entrectinib Safety Summary

- 203 patients have been treated at the RP2D across 3 clinical studies
- Most adverse events were Grade 1-2 and reversible
- Treatment-Related Adverse Events (TRAEs):
  - Leading to dose interruption: 32%
  - Leading to dose reduction: 19%
  - Serious Adverse Events: 9%
  - Leading to discontinuation from study treatment: 3%

<table>
<thead>
<tr>
<th>Most Common (≥10%) Treatment-Related Adverse Events, n (%)</th>
<th>Patients treated at the RP2D (N=203)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>78 (38)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>59 (29)</td>
</tr>
<tr>
<td>Constipation</td>
<td>47 (23)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>46 (23)</td>
</tr>
<tr>
<td>Weight increased</td>
<td>39 (19)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>35 (17)</td>
</tr>
<tr>
<td>Nausea</td>
<td>33 (16)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>32 (16)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>27 (13)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>25 (12)</td>
</tr>
<tr>
<td>Anemia</td>
<td>23 (11)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>22 (11)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>21 (10)</td>
</tr>
</tbody>
</table>

*There were no Grade 4 events occurring in >1% of patients; no Grade 5 TRAEs were reported.

Data cutoff date: 13 September 2017

RP2D=Recommended Phase 2 Dose

Ahn, WCLC 2017
Best Response to Entrectinib in ROS1 Fusion-Positive, Inhibitor-Naïve NSCLC

Three out of 32 patients had no post-baseline scans and were non-evaluable

Data cutoff date: 13 September 2017
Durability of Entrectinib Treatment in ROS1+ NSCLC Patients (by BICR)

Median DOR of 28.6 months (95% CI: 6.8, 34.8)

Median PFS of 29.6 months (95% CI: 7.7, 36.6)

Median follow-up: 12.9 months (5.6, 30.2)

Median follow-up: 8.5 months (5.4, 16.5)
Oncogene drivers in adenocarcinoma

Key
1 - Phase I 3 - Phase III
2 - Phase II 4 - Approved

EGFR Sensitizing
- Gefitinib
- Erlotinib
- Afatinib
- Osimertinib
- Nedatumab
- Rociletinib

ALK
- Crizotinib
- Alectinib
- Ceritinib
- Lorlatinib
- Brigatinib

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- Crizotinib
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HER2
- Trastuzumab emtansine
- Afatinib
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- Vemurafenib
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RET
- Cabozantinib
- Alectinib
- Apatinib
- Vandetanib
- Ponatinib
- Lenvatinib

NTRK1
- Entrectinib
- LOXO-101
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- DS-6051b

MEK1
- Trametinib
- Selumetinib
- Cobimetinib

PIK3CA
- LY3023414
- PQR 309

Unknown Oncogenic Driver Detected 31%
Oncogene drivers in adenocarcinoma
LOXO-292: potent and selective RET inhibition

- Rationally designed, informed by proprietary crystallography insights
- Highly selective
- Fusion- and mutation-independent RET inhibition
  - e.g. KIF5B-RET, CCDC6-RET
  - C634W, M918T, V804L/M (gatekeeper—acquired resistance)
- Favorable drug-like properties
LOXO-292 Phase 1 study in progress

- 28 patients enrolled to 4 dose levels (first patient dosed May 2017)
- No DLTs
- PK dose proportional and consistent with significant RET target engagement

September 27, 2017 data cut-off date, cellular (phospho-RET) IC$_{50}$/IC$_{90}$ corrected for human plasma protein binding
Systemic tumor response

Pre-treatment

LOXO-292 at 2 mo.

Velchetti, WCLC 2017
Intracranial tumor response

Pre-treatment

LOXO-292 at 3 mo.

Velchetti, WCLC 2017
EGFR Exon 20 insertion mutations have a low response rate to EGFR TKIs

Historical Data

<table>
<thead>
<tr>
<th></th>
<th>PD</th>
<th>SD</th>
<th>PR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geftinib/Erlotinib</td>
<td>28</td>
<td>4+1*</td>
<td>2*</td>
</tr>
<tr>
<td>Afatinib</td>
<td>9</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Totals</td>
<td>37</td>
<td>5</td>
<td>3</td>
</tr>
</tbody>
</table>

**ORR (with 763) = 8%**

**ORR (without 763) = 3%**

*A763insFQEA mutations

PD = Progressive Disease, SD = Stable Disease, PR = Partial Response, ORR = Overall Response Rate

Poziotinib induces partial response in 73% (8/11) of patients with EGFR Exon 20 mutations.
Take home message

• Osimertinib SOC EGFR mut NSCLC

• Alectinib SOC Alk mut NSCLC

• Dabra-Tremi SOC BRAF V600E mut NSCLC

• Nieuwe medicamenten in ontwikkeling tegen (nog) minder vaak (<1%) voorkomende drivers in NSCLC