Targeted treatment for HER addicted NSCLC
Why does it work (or not)

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Disclosures

• Advisor for AstraZeneca, BMS, Boehringer, Pfizer and MSD.

• Research grants from AstraZeneca, Boehringer, BMS and MSD.
Molecular alterations in NSCLC

- EGFR-sensitising (15%)
- EGFR other (2%)
- KRAS (25%)
- ALK (7%)
- HER2 (2%)
- BRAFV600E (2%)
- BRAF other (1%)
- ROS1 (2%)
- RET (2%)
- NTRK1 (0.5%)
- MET (3%)
- MAP2K1 (0.5%)
- PIK3CA (1%)
- NRAS (0.5%)
- >1 mutation (3%)
- Unknown (31%)

<table>
<thead>
<tr>
<th>History</th>
<th>Past</th>
<th>Present</th>
<th>(Near) Future</th>
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<tbody>
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<td>• SCLC</td>
<td>• HRM / PCR / FISH</td>
<td>• NGS</td>
<td>• WGS</td>
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<tr>
<td>• NSCLC</td>
<td>• EGFR</td>
<td>• Mutations</td>
<td>• Mutations</td>
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<td>• Adeno</td>
<td>• ALK</td>
<td>• Fusions</td>
<td>• Fusions</td>
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<td>• Sqaumous</td>
<td>• +/- selected other genes</td>
<td>• CNV</td>
<td>• CNV</td>
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<tr>
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<td>Age</td>
<td>Diagnosis</td>
<td>Smoking Status</td>
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<tr>
<td>Mevr. T, 43 jaar</td>
<td>• St IV NSCLC, never smoker</td>
<td>• EGFR mutation</td>
<td>• C.2235_2249del</td>
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<tr>
<td>Mevr. A, 43 jaar</td>
<td>• St IV NSCLC, never smoker</td>
<td>• EGFR mutation</td>
<td>• C.2300_2308dup</td>
</tr>
<tr>
<td>Mevr. W, 59 jaar</td>
<td>• St IV NSCLC, never smoker</td>
<td>• EGFR mutation</td>
<td>• C.2240_2257delins</td>
</tr>
</tbody>
</table>

c.2235_2249del
Mevr. A, 43 jaar. Erlotinib and later osimertinib

c.2300_2308dup
Mevr. W, 59 jaar. Erlotinib, later osimertinib, later afatinib

c.2240_2257delins
Mevr. W, 59 jaar  c.2240_2257delins
The Drug Rediscovery Protocol (DRUP trial)

Title

A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile.
DRUP Study: Trastuzumab-Pertuzumab
Mevr. A, 43 jaar  

c.2300_2308dup

- Female, 42 years old
- 2011: NSCLC LLL. Lobectomy, adj cis-pem.
- 2013: Cisplatin-pemetrexed. Best response: PR.
- 2015: Brain mets. WBRT.
- 03-2016: PD. Gemcitabin. Best response: SD.
- 06-2016: PD. Osimertinib. Best response: SD.
- 10-2016: PD. WHO PS 3, wheelchair, on oxygen treatment.
Molecular tumorboard meeting

- Molecular tumour board
  - (Thoracic) Oncologist
  - Pathologist
  - Clinical molecular biologist

- Sensitivity molecular alteration
- Clinical study available
- Type of treatment
- Location of treatment
Sensitivity molecular alteration
Mevr. A, 43 jaar

- Treatment with combination EGFR TKI and EGFR mAb
Osimertinib treatment for patients with EGFR exon 20 mutation positive non-small cell lung cancer

van Veggel B1, van der Wekken AJ2, Hashemi SMS3, Cornelissen R4, Monkhorst K5, Heideman DAM6, Radonic T5, Schuring E7, Smit EF1,2, de Langen AJ1

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Abstract 14182

Introduction

- Epidermal growth factor receptor (EGFR) exon 20 insertion mutations are identified in 9-12% of all EGFR mutations in non-small cell lung cancer (NSCLC). [1,2]
- EGFR exon 20 mutations are associated with primary resistance to first and second generation EGFR tyrosine kinase inhibitors (TKIs). [3,4]
- In vitro and preclinical animal studies have shown that osimertinib, a third generation EGFR TKI, exerts antitumor activity in EGFR exon 20 insertion positive NSCLC. [5]
- We report on a cohort of 20 patients with advanced stage EGFR exon 20 mutation positive NSCLC that were treated with osimertinib.

Methods

- 20 patients with advanced NSCLC harboring an EGFR exon 20 mutation were treated with osimertinib 80 mg once daily, in four institutions in the Netherlands.
- Data were obtained retrospectively.
- EGFR mutation status was assessed by next-generation sequencing.
- Objective response rate (ORR), progression-free survival (PFS) and disease control rate (DCR) at five months were assessed according to RECIST v1.1.

Results

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>n=20 (%)</th>
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</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>62 (range 45-80)</td>
</tr>
<tr>
<td>Sex</td>
<td>M:13 (65%)</td>
</tr>
<tr>
<td>EGFR mutation</td>
<td>L858R</td>
</tr>
<tr>
<td>Number of lines for advanced disease</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Prior platinum-based chemotherapy</td>
<td>12 (60%)</td>
</tr>
<tr>
<td>Prior TKI Type</td>
<td>First generation</td>
</tr>
<tr>
<td>First generation</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>12 (60%)</td>
</tr>
</tbody>
</table>

Figure 1. Waterfall plot of best percentage change in tumor size during osimertinib treatment

| ORR 5.6% |
| Partial response |
| Stable disease |
| Progressive disease |

Table 2. Response to treatment

<table>
<thead>
<tr>
<th>Mutation type</th>
<th>Best response</th>
<th>PFS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PD</td>
<td>1.7</td>
</tr>
<tr>
<td>2</td>
<td>PD</td>
<td>0.7</td>
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<tr>
<td>3</td>
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<td>4</td>
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</tr>
<tr>
<td>5</td>
<td>PD</td>
<td>3.8</td>
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<tr>
<td>6</td>
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</tr>
<tr>
<td>7</td>
<td>PD</td>
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</tr>
<tr>
<td>8</td>
<td>PD</td>
<td>3.0</td>
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<tr>
<td>9</td>
<td>PD</td>
<td>1.7</td>
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<tr>
<td>10</td>
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<td>3.2</td>
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<tr>
<td>11</td>
<td>PD</td>
<td>2.7</td>
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<td>12</td>
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<td>13</td>
<td>PD</td>
<td>1.4</td>
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</table>

Conclusions

- Osimertinib has limited antitumor activity in patients with EGFR exon 20 mutated NSCLC, with an ORR of 5.6%.
- Durable responses (25 months) were seen in 35% of patients.
- One patient experienced a partial response during osimertinib treatment. This patient harbored an EGFR exon 20 nucleotide substitution.

References


Corresponding author: b.v.veggel@vki.nl
58 jarige man, EGFR p.His773_Val774DelinsLeuMet

- 06-2017 SRS on oligoprogression of brain met.
- 11-2017 PD in and outside the brain. Re-WBRT and referral
Phase II trial of poziotinib for EGFR and HER2 exon 20 mutant NSCLC


University of Texas MD Anderson Cancer Center
Pozotinib efficacy in EGFR Exon 20 mutant NSCLC
(Evaluable patients n=44)

ORR (best response): 55%
ORR (confirmed): 43%

Germline T790M +exon20ins

* Remains on treatment

Progressive Disease (PD)
Stable Disease (SD)
Partial Response (PR)
Response not confirmed/ Follow-up Pending
EGFR exon 20 insertion positive NSCLC

- No registered medication.
- Heterogeneous population

- Poziotinib
- TAK-788
- TAS-6417
- Afatinib-Cetuximab
- Osimertinib

Mevr. T, 43 jaar  
c.2235_2249del

- 10-2014: Gefitinib. Best response: PR
Mevr. T, 43 jaar

- 10-2014: Gefitinib. Best response: PR
- 12-2016: PD.
Merv. T, 59 jaar

- **Plasma**
  - EGFR exon 19 del 127 copies/ml plasma. EGFR exon 20 T790M not detectable.

- **Biopsy**
  - PD-L1 IHC: 100% positive.
Mevr. T, 59 jaar
Osimertinib and Crizotinib treatment (EGFR and MET TKI)

Resistance in the resistance

Resistance – analysis beyond mutations

- Allelic frequency of resistance
- Allelic contexture of mutations
Mevr. E, 79 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- C.2235_2249del
- Erlotinib treatment
- c.2369C>T p.Thr790Met (p.T790M)
- Osimertinib treatment
- c.2390G>C p.Cys797Ser (p.C797S)

Mevr. G, 68 jaar

- St IV NSCLC, never smoker
- EGFR mutation
- C.2235_2249del
- Erlotinib treatment
- c.2369C>T p.Thr790Met (p.T790M)
- Osimertinib treatment
- c.2390G>C p.Cys797Ser (p.C797S)
Mevr. E, 79 jaar

- EGFR c.2235_2249del p.Glu746_Ala750del (p.E746_A750del). AF 64%
- EGFR c.2369C>T p.Thr790Met (p.T790M). AF 20%
- EGFR c.2389T>A p.Cys797Ser (p.C797S). AF 15%
- De EGFR codon 797 mutatie ligt in trans met p.T790M.
- TP53 c.216delC p.Val73fs (p.V73fs) AF 30%
- RB1 c.2077G>T p.Glu693* (p.E693*) AF 89%

Mevr. G, 68 jaar

- EGFR c.2235_2249del p.Glu746_Ala750del (p.E746_A750del). AF 74%
- EGFR c.2369C>T p.Thr790Met (p.T790M). AF 30%
- EGFR c.2389T>A p.Cys797Ser (p.C797S). AF 31%
- De EGFR codon 797 mutatie ligt in cis met p.T790M.
- Amplificatie van het EGFR gen. Z-score = 6.8
- CTNNB1 c.134C>T p.Ser45Phe (p.S45F). AF 100%.
Molecular tumorboard meeting

- Molecular tumour board
  - (Thoracic) Oncologist
  - Pathologist
  - Clinical molecular biologist

- Sensitivity molecular alteration
- Clinical study available
- Type of treatment
- Location of treatment
Schematic representation of EGFR resistance mutations in response to TKI treatment and sensitivity to subsequent therapies.

Mevr. E, 79 jaar – Erlotinib + Osimertinib
Mevr. E, 79 jaar – Erlotinib + Osimertinib
Resistance mechanisms to osimertinib

• On target
  • Tertiary EGFR mutations
  • EGFR amplification

• Vertical resistance
  • BRAF V600E mutation
  • KRAS mutations
  • KRAS amplification

• Horizontal resistance
  • MET amplification
  • HER2 amplification
  • HER2 mutation
  • ALK translocation
  • ROS1 translocation
  • RET translocation
  • FGFR-1 amplification
HER2 driven NSCLC

- HER2 mutation (mainly exon 20 insertions)
- HER2 amplification
- HER2 overexpression
46 year old male patient

- 01-2017: St IV NSCLC, TTF-1+ adenocarcinoma, primary LUL with mediastinal, hilar and axillary Inn mets and lung mets.
- COPD Gold 3
- Drug abuse
- Bronchiectasis
- Smoking history: 30 PY
- Currently being screened for tuberculosis
46 year old male patient

• Pathology:
  • NGS: RB1, TP53, SMO mutations, HER2 copy number gain
  • IHC: HER2 100% 3+ intensity staining
  • IHC: PD-L1 0%
  • FISH: HER2 >10 gene copies / nucleus.
The Drug Rediscovery Protocol (DRUP trial)

Title
A Dutch National Study on behalf of the Center for Personalized Cancer Treatment (CPCT) to Facilitate Patient Access to Commercially Available, Targeted Anti-cancer Drugs to determine the Potential Efficacy in Treatment of Advanced Cancers with a Known Molecular Profile.
### DRUP Study: Trastuzumab-Pertuzumab

![CT scans](image)

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<td>-</td>
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<td>H Hemolyt.</td>
<td>-</td>
<td>-</td>
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</table>
56 year old female patient

- 06-2018: PD.
- 07-2018: screening for DRUP study in trastuzumab / pertuzumab
Molecular tumor board meeting

- Molecular tumour board
  - (Thoracic) Oncologist
  - Pathologist
  - Clinical molecular biologist

- Sensitivity molecular alteration
- Clinical study available
- Type of treatment
- Location of treatment
Pozotinib efficacy in HER2 Exon 20 insertion mutant NSCLC

Best response HER2
(Evaluable patients n=12)

Progression-free Survival HER2
(All patients n=13)

Median PFS 5.1 months

Y772dupYVA
Y772dupYVA
Y772dupYVA
G778dupGSP
Y772dupYVA
Y772dupYVA
Y772dupYVA
Y772dupYVA
Y772dupYVA
Y772dupYVA
Y772dupYVA
Y772dupYVA

* Remains on treatment
HER2 exon 20 insertion positive NSCLC

• No registered medication.
• Heterogeneous population

• Poziotinib
• T-DM1
• TAK-788
Conclusions

• It all starts with finding the oncogenic driver or driver of resistance
• Test everything anytime (mutations, CNV and fusions)
• Allelic frequency
• Allelic contexture
• Concurrent molecular alterations
• Molecular tumorboard
• Chemo-immunotherapy is just as important as targeted treatment.
• Treat in clinical studies wherever possible
Thank you for listening

Questions?