Hermes project: implementing EGFR mutation analysis in clinical care in Antwerp

E. De Droogh, A. Janssens & A. Lefebure

1st line EGFR-TKI vs chemotherapy in EGFR mutation positive NSCLC

<table>
<thead>
<tr>
<th>Trial</th>
<th>RR</th>
<th>PFS (m)</th>
<th>HR PFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPASS subgroup</td>
<td>71% vs 47%</td>
<td>9.6 m vs 6.3 m</td>
<td>0.48</td>
</tr>
<tr>
<td>WJTOG3405</td>
<td>62% vs 31%</td>
<td>9.2 m vs 6.3 m</td>
<td>0.49</td>
</tr>
<tr>
<td>NEJ002</td>
<td>74% vs 31%</td>
<td>10.8 m vs 5.4 m</td>
<td>0.30</td>
</tr>
<tr>
<td>OPTIMAL</td>
<td>83% vs 36%</td>
<td>14.7 m vs 4.6 m</td>
<td>0.16</td>
</tr>
<tr>
<td>EURTAC</td>
<td>59% vs 15%</td>
<td>9.7 m vs 5.2 m</td>
<td>0.57</td>
</tr>
</tbody>
</table>

EGFR-TKI as 1st-line treatment for NSCLC with activating EGFR mutations?

- Improved progression free survival
- Improved response rate
- Improved QoL and symptom control
- Favourable toxicity profile
- Following 1st line chemotherapy ±1/3 of pts receive no further treatment

→ gefitinib is the new standard of care for the 1st-line treatment for NSCLC with activating EGFR mutations!

Hermes project

Aims:
- to establish a “regional network” for the analysis of molecular tumor markers (i.e. EGFR mutation status)
- to optimize the logistics of such a network for molecular tumor analysis:
  - Ideally the results should be available in all patients within 2 weeks of the analysis request.
- to obtain an epidemiologic description of the molecular tumor characteristics (i.e. EGFR mutation status) in Antwerp
Hermes project

**Aim:**
- to establish a “regional network” for the analysis of molecular tumor markers (i.e. EGFR mutation status)
- to optimize the logistics of such a network for molecular tumor analysis

- **Pneumo-oncologist or Medical oncologist**
- **Local pathology lab**
- **Centralized EGFR-mutation analysis**
- **Shipping of tumor samples**
- **Reporting of mutation analysis**
- **≤ 14 d**

**Primary endpoints:**
- time to get the mutation analysis results
  - time from oncologist to local pathology
  - time from local pathology to molecular analysis lab
  - time from molecular analysis lab to oncologist

**Secondary endpoints:**
- epidemiologic description of the molecular tumor characteristics (i.e. EGFR mutation status) in Antwerp
- “exploratory analysis” of the relationship between the pulmonary function and incidence of EGFR mutation

**Hermes project: patient characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Number (n)</th>
<th>Median (range)</th>
<th>Male</th>
<th>Female</th>
<th>Caucasian</th>
<th>Asian</th>
<th>North African</th>
<th>Smoker</th>
<th>Ex-smoker</th>
<th>Never smoker</th>
<th>Performance status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (n 107)</td>
<td></td>
<td>65 yr (44-90 yr)</td>
<td>68 (64%)</td>
<td>39 (36%)</td>
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<tr>
<td><strong>Gender</strong> (n 107)</td>
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<td></td>
<td></td>
<td>104 (97%)</td>
<td>1 (1%)</td>
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<td>45 (42%)</td>
<td>49 (46%)</td>
<td>13 (12%)</td>
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<tr>
<td><strong>Ethnicity</strong> (n 106)</td>
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</tr>
<tr>
<td>Caucasian</td>
<td></td>
<td>104 (97%)</td>
<td></td>
<td></td>
<td>1 (1%)</td>
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<tr>
<td>Asian</td>
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<td>1 (1%)</td>
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<tr>
<td>North African</td>
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<td>1 (1%)</td>
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<tr>
<td><strong>Smoking status</strong> (n 106)</td>
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<tr>
<td>Smoker</td>
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<td>45 (42%)</td>
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<tr>
<td>Ex-smoker</td>
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<td>49 (46%)</td>
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<tr>
<td>Never smoker</td>
<td></td>
<td>13 (12%)</td>
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<tr>
<td><strong>Performance status</strong> (n 97)</td>
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<td></td>
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<tr>
<td>PS 0</td>
<td></td>
<td>38 (39%)</td>
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<tr>
<td>PS 1</td>
<td></td>
<td>50 (52%)</td>
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<tr>
<td>PS 2</td>
<td></td>
<td>9 (9%)</td>
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</tbody>
</table>

**Hermes project: participating hospitals**

<table>
<thead>
<tr>
<th>Hospital</th>
<th>Number of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>GZA-St. Jozef</td>
<td>21</td>
</tr>
<tr>
<td>UZ Leuven</td>
<td>14</td>
</tr>
<tr>
<td>AZ St. Vincentius</td>
<td>14</td>
</tr>
<tr>
<td>UZ Steenhoven</td>
<td>13</td>
</tr>
<tr>
<td>AZ Erasmus</td>
<td>11</td>
</tr>
<tr>
<td>AZ Middelheim</td>
<td>10</td>
</tr>
<tr>
<td>AZ Middelheim</td>
<td>8</td>
</tr>
<tr>
<td>AZ Meiseles</td>
<td>7</td>
</tr>
<tr>
<td>AZ St. Jozef</td>
<td>6</td>
</tr>
<tr>
<td>AZ St. Jozef</td>
<td>2</td>
</tr>
<tr>
<td>AZ St. Jozef</td>
<td>1</td>
</tr>
</tbody>
</table>
Hermes project: biopsy characteristics

<table>
<thead>
<tr>
<th>Tumor biopsy type (n=107)</th>
<th>Cytology</th>
<th>Percutaneous needle biopsy</th>
<th>EUS FNA</th>
<th>EBUS TBNA</th>
<th>Bronchoscopic biopsy</th>
<th>Mediastinoscopic biopsy</th>
<th>Surgical biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>20</td>
<td>1</td>
<td>6</td>
<td>33</td>
<td>6</td>
<td>33</td>
</tr>
</tbody>
</table>

Hermes project: tumor characteristics

<table>
<thead>
<tr>
<th>Tumor Histology (n=104)</th>
<th>Adenocarcinoma</th>
<th>Large cell carcinoma</th>
<th>NSCLC NOS</th>
<th>Squamous cell carcinoma</th>
<th>Small cell carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>84</td>
<td>1</td>
<td>5</td>
<td>13</td>
<td>1</td>
</tr>
</tbody>
</table>

EGFR mutation analysis (n=107)

- EGFR wild type: 95
- EGFR activating mutation: 7
- EGFR analysis not possible: 5

Hermes project: tumor characteristics

EGFR mutations (n=7)

- Exon 19 deletion: 6
- Exon 21 L858R mutation: 1

Gender Incidence

- Male: 4 (7%)
- Female: 3 (8%)

Smoking status

- Smoker: 2 (4%)
- Ex-smoker: 3 (6%)
- Never: 2 (5%)

Ethnicity

- Caucasian: 6 (6%)
- Asian: 1 (6%)

Histology

- AdenoCA: 7 (8%)

Hermes project: EGFR-mutations in non-asians with non-squamous carcinoma (N89)

EGFR mutations (n=6)

- Exon 19 deletion: 5
- Exon 21 L858R mutation: 1

Gender Incidence

- Male (n=56): 4 (7%)
- Female (n=33): 2 (6%)

Smoking status

- Smoker (n=39): 2 (5%)
- Ex-smoker (n=39): 3 (8%)
- Never (n=10): 1 (10%)

Hermes project: median time (range) of each step

<table>
<thead>
<tr>
<th>Step</th>
<th>Oncologist</th>
<th>Local path lab</th>
<th>Central lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1</td>
<td>5d (0-23d)</td>
<td>6d (0-23d)</td>
<td>5d (0-23d)</td>
</tr>
<tr>
<td>Step 2</td>
<td>6d (0-15d)</td>
<td>6d (0-15d)</td>
<td>5d (0-15d)</td>
</tr>
<tr>
<td>Step 3</td>
<td>6d (0-15d)</td>
<td>6d (0-15d)</td>
<td>5d (0-15d)</td>
</tr>
<tr>
<td>Step 4</td>
<td>6d (0-23d)</td>
<td>6d (0-23d)</td>
<td>5d (0-23d)</td>
</tr>
</tbody>
</table>

Total processing time median mean range

- Result via local path lab: 10 d 12 d 3-37 d
- Result via central lab: 9 d 11 d 3-29 d

Hermes project: interdepartmental communication steps & intradepartmental processing steps
Hermes project: processing times in 1\(^{st}\) two months of project (n 24)

<table>
<thead>
<tr>
<th></th>
<th>Result via local path lab</th>
<th>Result via central lab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total processing time</strong></td>
<td>14 d (10-22 d)</td>
<td>10 d (8-17 d)</td>
</tr>
<tr>
<td><strong>Median 25-75 % range</strong></td>
<td>7-17 d</td>
<td>4-29 d</td>
</tr>
</tbody>
</table>

Hermes project: processing times after 1\(^{st}\) two months of project (n 83)

<table>
<thead>
<tr>
<th></th>
<th>Result via local path lab</th>
<th>Result via central lab</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total processing time</strong></td>
<td>9 d (7-12 d)</td>
<td>8 d (7-12 d)</td>
</tr>
<tr>
<td><strong>Median 25-75 % range</strong></td>
<td>2-22 d</td>
<td>3-28 d</td>
</tr>
</tbody>
</table>

Hermes project: processing times before and after 1\(^{st}\) two months

<table>
<thead>
<tr>
<th></th>
<th><strong>Total time local lab</strong></th>
<th><strong>Total time central lab</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median 25-75 %</strong></td>
<td><strong>Median 25-75 %</strong></td>
<td></td>
</tr>
<tr>
<td>1(^{st}) two months</td>
<td>14 d (10-22 d)</td>
<td>10 d (8-17 d)</td>
</tr>
<tr>
<td>After 1(^{st}) two months</td>
<td>9 d (7-12 d)</td>
<td>8 d (7-12 d)</td>
</tr>
</tbody>
</table>

Hermes project: difference between local and central lab reporting

- Faster reporting through central lab
- Faster reporting through local lab

EGFR Gene Alterations in a Norwegian Cohort of Lung Cancer Patients Selected for Surgery

<table>
<thead>
<tr>
<th>EGFR mutations: in 18/240 or 7.5% of samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exon 18 G719X mutation 1</td>
</tr>
<tr>
<td>Exon 19 deletion 8</td>
</tr>
<tr>
<td>Exon 20 insertion 3</td>
</tr>
<tr>
<td>Exon 21 L858R mutation 5</td>
</tr>
<tr>
<td>Exon 21 L861Q mutation 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender</th>
<th><strong>Male</strong></th>
<th><strong>Female</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td>22%</td>
<td>78%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Smoking history</th>
<th><strong>Ever-smoker</strong></th>
<th><strong>Never smoker</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td>44%</td>
<td>56%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Histology</th>
<th><strong>Adenocarcinoma</strong></th>
<th><strong>Squamous cell</strong></th>
<th><strong>SAC</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>%</strong></td>
<td>78%</td>
<td>11%</td>
<td>11%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Incidence of EGFR Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers

- 2,142 samples were tested.
- EGFR mutations were found in:
  - 6% of tumors from current smokers
  - 15% of tumors from former smokers
  - 52% of tumors from never smokers
  - 19% of tumors from men
  - 26% of tumors from women
Incidence of EGFR Exon 19 deletions and L858R in lung adenocarcinomas from men and smokers

If only women who were never smokers were tested, 57% of all EGFR mutations would be missed.


BESLUIT

- Snelle implementatie van EGFR mutatie testing met gemiddeld na 14 dagen resultaat.
- EGFR mutatie testen bij alle non-squamous onafhankelijk van het geslacht en rokerstatus.

Hermes project

Step 1

Step 2

Step 3

Step 4

Step 5
**Hermes project: tumor characteristics**

<table>
<thead>
<tr>
<th>EGFR mutations (n 7)</th>
<th>Exon 19 deletion</th>
<th>Exon 21 L858R mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Biopsy type</td>
<td>Lung resection</td>
<td>Bronchoscopic biopsy</td>
</tr>
<tr>
<td>Smoking history</td>
<td>Smoker</td>
<td>Never smoker</td>
</tr>
<tr>
<td>Ethnicity</td>
<td>Caucasian</td>
<td>Asian</td>
</tr>
<tr>
<td>Histology</td>
<td>Adenocarcinoma</td>
<td></td>
</tr>
</tbody>
</table>

**Hermes project: tumor characteristic:**

<table>
<thead>
<tr>
<th>Tumor biopsy type (n 107)</th>
<th>Cytopology</th>
<th>Percutaneous needle biopsy</th>
<th>EUS FNA</th>
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<th>Mediastinoscopic biopsy</th>
<th>Surgical biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>84</td>
<td>20</td>
<td>1</td>
<td>6</td>
<td>33</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>Large cell carcinoma</td>
<td>1</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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</tr>
<tr>
<td>NSCLC NOS</td>
<td>5</td>
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<td></td>
</tr>
<tr>
<td>Squamous cell carcinoma</td>
<td>13</td>
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<tr>
<td>Small cell carcinoma</td>
<td>1</td>
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</table>

**EGFR Gene Alterations in a Norwegian Cohort of Lung Cancer Patients Selected for Surgery**

- **EGFR-mutation detected in 18/240 or 7.5% of samples**

**Genotypic and Histological Evolution of NSCLCs Acquiring Resistance to EGFR Inhibitors**

- All drug-resistant tumors retained their original activating EGFR mutations
- In 10% of patients, serial biopsies revealed that genetic mechanisms of resistance were lost in the absence of the continued selective pressure of EGFR inhibitor treatment, and such cancers were sensitive to a second round of treatment with EGFR inhibitors.