Clinical pharmacology of genotype-directed anticancer therapy

Towards rational combination strategies

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AIOS ziekenhuisfarmacie

Disclosure belangen spreker

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<thead>
<tr>
<th>(potentiële) belangenverstrengeling</th>
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<tr>
<td>Voor bijeenkomst mogelijk relevante relaties met bedrijven</td>
<td>Bedrijfsnamen</td>
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<td>• Sponsoring of onderzoeksgeld</td>
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<td>• Honorarium of andere (financiële) vergoeding</td>
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<td>• Andere relatie, namelijk …</td>
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‘One treatment fits all’ versus genotype-directed therapy

Patients with metastatic colon cancer

MAPK pathway and frequent oncogenic mutations

\[ \text{BRAF} \text{ mutation incidence} \]
- Melanoma (60%)
- Colorectal (12%)

Adapted from: Dhillon et al. Oncogene 2007;26:3279-90
Introduction in colorectal cancer (CRC)

- Approximately 14,000 new CRC patients each year in NL
  - 25% present with metastases at initial diagnosis
  - 25% will develop metastases

- Treatment options in metastatic setting
  - 1st line: 5-FU/oxaliplatin-based chemotherapy (+ bevacizumab)
  - 2nd line: Irinotecan chemotherapy
  - 3rd line: Monoclonal antibody targeting EGFR: cetuximab or panitumumab → for RAS wild-type patients

- 5-year survival rate of patients with metastatic CRC (mCRC): ~13%
  - <5% in patients with BRAF mutation


BRAF inhibition in melanoma versus colorectal cancer

Vemurafenib response rate in BRAFm melanoma versus CRC

~50%

EGFR-mediated reactivation of PI3K and MAPK pathways upon BRAF inhibition in BRAFm CRC

Results phase Ib study – encorafenib plus cetuximab in BRAFm CRC
Adverse events, suspected to be drug-related

<table>
<thead>
<tr>
<th></th>
<th>Encorafenib + Cetuximab (n = 26)</th>
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<tr>
<td>AE, n (%)</td>
<td>All Grades</td>
</tr>
<tr>
<td>Total</td>
<td>21 (81)</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (27)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (8)</td>
</tr>
<tr>
<td>Rash acneiform</td>
<td>5 (19)</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>1 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6 (23)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>11 (42)</td>
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<tr>
<td>Discontinuation due to AEs</td>
<td>3 (11%)</td>
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Results phase Ib study – encorafenib plus cetuximab in *BRAF*m CRC

**Antitumor activity**

- Overall response rate: 23%
- Disease control rate: 77%

**Threshold for Response According to RECIST**

- Complete response (CR)
- Partial response (PR)
- Stable disease (SD)
- Progressive disease (PD)


Results phase Ib study – encorafenib plus cetuximab in *BRAF*m CRC

**Antitumor activity**

**Progression-free survival, weeks**

Overall survival phase II study vs. historical controls

Conclusions and future perspectives

- Unmet medical need for patients with BRAFm CRC

- BRAFm CRC is unresponsive to BRAF inhibitor monotherapy

- Concurrent BRAF + EGFR inhibition is safe and tolerable

- Promising clinical activity in Phase Ib and Phase II

- Phase III study (worldwide) started in Q4 2016
  - Encorafenib + cetuximab vs. second line standard chemotherapy
Conclusions and future perspectives

- Primary and acquired resistance limits efficacy genotype-directed therapy
- Combinations are necessary to overcome escape mechanisms!

Van pole position naar podium

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