Personalized treatment in NSCLC: fact or fiction?

Paul Germonpré
Personalized treatment in NSCLC

• Aims and challenges of biomarker driven treatment
• Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    • EGFR-TKIs
    • Anti-VEGF
  - Chemotherapy:
    • Pemetrexed
    • Cisplatin-based chemotherapy
• Treatment customized on patient genotype markers
  • Gemcitabine
  • Paclitaxel
Treatment selection in NSCLC

**Tumor characteristics**
- TNM-stage

**Patient characteristics**
- Performance status
- Age and comorbidities

**Patient preference**
- Toxicities
- Treatment administration

**Doctor preference**
- Experience with drug
Development of Personalized Therapy for NSCLC

Aims of personalized cancer care

• **Individual patient level**
  - selection of treatment based on the biology and molecular characteristics of the patient as well as the tumor in order to:
    • improve the efficacy of the treatment and/or
    • avoid life threatening toxicity

• **Society level**
  - reduction of the cost of cancer care by
    • restricting the treatment to the patients most likely to benefit
    • avoiding ineffective treatments
    • reducing morbidity and complications
Prognostic versus predictive markers

**Prognostic**
Provides information on outcome, regardless of treatment

**Predictive**
Provides information on outcome with regards to a specific therapy

Many biomarkers have both prognostic and predictive value

Controlled trials or meta-analyses are required to determine the prognostic and predictive contributions made by a particular marker
Requirements on the trial design for identifying a predictive biomarker

Hypothesis generating

Open label
Small numbers
Single arm

Retrospective analysis
Non-stratified

Hypothesis testing

Double-blind randomized
Placebo-controlled
Adequately powered
Prospective analysis
Stratified by biomarker status
# Moving towards customized treatment

| Tumor characteristics | • TNM-stage  
| | • **Tumor biomarkers**  
| Patient characteristics | • Performance status  
| | • Age and comorbidities  
| | • **Patient biomarkers**  
| Patient preference | • Toxicities  
| | • Treatment administration  
| Doctor preference | • Experience with drug  

![Diagram showing diverse populations with labels for tumor characteristics, patient characteristics, patient preference, and doctor preference]
Personalized treatment in NSCLC

- Aims and challenges of biomarker driven treatment
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  - Chemotherapy:
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  • Gemcitabine
  • Paclitaxel
Signal Transduction Pathways Controlled by the Activation of EGFR

BR.21: predictors of response

<table>
<thead>
<tr>
<th></th>
<th>Erlotinib Patients (%)</th>
<th>p*</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>(n=427)</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (146)</td>
<td>14.4</td>
<td>0.006</td>
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<tr>
<td>Male (281)</td>
<td>6.1</td>
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<tr>
<td>Histology</td>
<td></td>
<td></td>
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<tr>
<td>Adenocarcinoma (209)</td>
<td>13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other (218)</td>
<td>4.1</td>
<td></td>
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<tr>
<td>Ethnicity</td>
<td></td>
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</tr>
<tr>
<td>Asian (53)</td>
<td>18.9</td>
<td>0.02</td>
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<td>Other (374)</td>
<td>7.5</td>
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<tr>
<td>Ever smoked</td>
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<tr>
<td>Yes (311)</td>
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<td>No (93)</td>
<td>24.7</td>
<td>&lt;0.001</td>
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<tr>
<td>Unknown (23)</td>
<td>13.0</td>
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</table>

*Significance between subgroups
BR.21: overall survival ~ clinical predictors for response (EGFR mutation)

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>CI</th>
<th>p*</th>
</tr>
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<tbody>
<tr>
<td><strong>Gender</strong></td>
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<tr>
<td>Male (475)</td>
<td>0.8</td>
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<tr>
<td>Female (256)</td>
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<td>0.6–1.1</td>
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<tr>
<td><strong>Histology</strong></td>
<td></td>
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<tr>
<td>Adenocarcinoma (365)</td>
<td>0.7</td>
<td>0.6–0.9</td>
<td>0.37</td>
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<tr>
<td>Other (366)</td>
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<td>0.6–1.0</td>
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<tr>
<td><strong>Ethnicity</strong></td>
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<tr>
<td>Asian (91)</td>
<td>0.6</td>
<td>0.4–1.0</td>
<td>0.44</td>
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<td>Other (640)</td>
<td>0.8</td>
<td>0.7–0.9</td>
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<td><strong>Smoking history</strong></td>
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<td>Ever (545)</td>
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<td>0.7–1.0</td>
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<tr>
<td>Never (146)</td>
<td>0.4</td>
<td>0.3–0.6</td>
<td>0.02</td>
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<tr>
<td>Unknown (40)</td>
<td>1.1</td>
<td>0.5–2.6</td>
<td></td>
</tr>
</tbody>
</table>

*p value for interaction between erlotinib and clinical variables

Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

>80% of EGFR mutations; results in constitutive EGFR activation

Constitutively active TK (ligand independent)

associated with acquired resistance to EGFR-TKI

**IPASS : 1st line EGFR-TKI vs chemotherapy**

**Inclusion criteria:**
- Chemonaive Asian pts
- Adenocarcinoma
- Never or light ex-smokers

**Statistics:** PFS as primary endpoint

**Gefitinib arm:** Gefitinib 250 mg/d until PD

**Chemotherapy arm:** Carboplatin + Paclitaxel (6 cycles)

---

Mok et al. NEJM 2009; 361:947-57.
IPASS: Progression-free survival

**EGFR-mutation positive**
- Gefitinib: 71% *
- Carbo/Paclitaxel: 47%
- Median PFS: 9.6 m *

**EGFR-mutation negative**
- Gefitinib: 1%
- Carbo/Paclitaxel: 23%
- Median PFS: 1.5 m, 5.5 m *

---

* P < 0.05

Mok et al. NEJM 2009; 361:947-57.
IPASS: Overall survival

**EGFR-mutation positive**

**EGFR-mutation negative**

The presence of an EGFR mutation:
- is a strong predictive biomarker for response rate (both to chemotherapy and EGFR-TKI)
- is a strong predictive biomarker for PFS with EGFR-TKI versus chemotherapy
- is a favourable prognostic factor

At progression ~40% of patients in each arm crossed over to other treatment modality
WJTOG3405: 1st line gefitinib vs chemotherapy

Inclusion criteria:
• Chemonaive Asian pts
• EGFR activating mutation

Statistics: PFS as primary endpoint

Gefitinib arm: Gefitinib 250 mg/d until PD
Chemotherapy arm: Cisplatin + Docetaxel (6 cycles)

Mitsudomi et al. Lancet: DOI:10.1016/S1470-2045(09)70364-X.
SATURN: erlotinib as maintenance in 1st-line treatment of advanced NSCLC

Inclusion criteria:
- Stage IIIB/IV NSCLC
- PS 0-1
- Non-PD following 4 cycles of platinum-based chemotherapy*

Statistics: PFS as primary endpoint

Maintenance arm (n=438):
Erlotinib 150 mg/d until PD

Control arm (n=451):
Placebo 1x/d until PD

* 1st line chemotherapy: Cisplatin/Carboplatin + Docetaxel/Paclitaxel/Gemcitabine/Vinorelbine

Cappuzzo et al. ASCO 2009: abstract 8001.
EGFR mutations identify patients who derive a great PFS-benefit from erlotinib maintenance (median PFS 45 wks vs 13 wks).
**SATURN: overall survival**

**EGFR-wild type**

HR = 0.77 (0.61–0.97)  
Log-rank p = 0.0243

**EGFR-mutation positive** *

HR = 0.83 (0.34–2.02)  
Log-rank p = 0.6810

*67% of patients with EGFR mutation+ disease in the placebo arm received a second-line EGFR TKI*

Brugger, et al. WCLC 2009
Signal Transduction Pathways Controlled by the Activation of EGFR

Ciardiello and Tortora. NEJM. 2008; 358:1160-74.
NSCLC: driver mutations

Genetic alterations responsible for initiating and maintaining lung cancer:

- Squam.Ca
  - EGFR mutations (10-40%)
- AdenoCA
  - KRAS mutations (10-30%)
  - EML4-ALK fusion (~10%)
- Large cell CA
  - other
ALK gene rearrangements and crizotinib in NSCLC

- ALK gene rearrangements:
  - occur in 3-5% of unselected NSCLC
  - higher frequency in adenoCA in light or never smokers
- Crizotinib (PF-02341066):
  - potent oral inhibitor of ALK and MET
- Phase I-II trial of crizotinib:
  - heavily pre-treated NSCLC with proven FISH-positive ALK rearrangement
  - symptomatic improvements occur within 3 days
  - in 50 evaluable pts:
    - objective response rate 64%
    - disease control rate 90%

→ Phase III initiated
Bevacizumab and NSCLC

• **Randomized phase 2 trial of carbo-pacli ± bevacizumab:**
  - incidence of life-threatening pulmonary hemorrhage:
    • 9% in all bevacizumab-treated patients
    • 31% in pts with squamous cell cancer
    • 4% in pts with adenocarcinoma
  → the phase 3 studies enrolled only non-squamous-cell NSCLC.

• **EMEA label:**
  bevacizumab, in addition to platinum-based chemotherapy, is indicated for 1st-line treatment of patients with unresectable advanced, metastatic or recurrent NSCLC other than predominantly squamous cell histology.

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  - Gemcitabine
  - Paclitaxel
Cisplatin+Pemetrexed vs Cisplatin+Gemcitabine in 1st-line treatment of advanced NSCLC

Inclusion criteria:
- Chemo-naïve advanced NSCLC
- PS 0-2
- No CNS metastasis

* every 3 weeks for 6 cycles

Cis-Pem arm *
- Cisplatin 75 mg/m2 d1
- Pemetrexed 500 mg/m2 d1

Cis-Gem arm *
- Cisplatin 75 mg/m2 d1
- Gemcitabine 1250 mg/m2 d1,8

ITT population

<table>
<thead>
<tr>
<th></th>
<th>C-P</th>
<th>C-G</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (m)</td>
<td>10.3</td>
<td>10.3</td>
<td>0.94</td>
</tr>
</tbody>
</table>

Cisplatin+Pemetrexed vs Cisplatin+Gemcitabine in 1st-line treatment of advanced NSCLC

Non-squamous patients

Squamous patients

Pemetrexed as maintenance in 1\textsuperscript{st}-line treatment of advanced NSCLC

**Inclusion criteria:**
- PS 0-1
- Non-progressing following 4 cycles of platinum + gemcit, doc or pacli

**Maintenance arm:**
Pemetrexed 500 mg/m\textsuperscript{2} Q3wks* until PD (n=441)

**Control arm:**
Placebo d1 Q3wks* until PD (n=222)

*Vitamin B12, folate and dexamethasone given in both arms

<table>
<thead>
<tr>
<th>ITT population</th>
<th>Pem</th>
<th>Plac</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (m)</td>
<td>15.5</td>
<td>10.3</td>
<td>.012</td>
</tr>
</tbody>
</table>
Pemetrexed maintenance trial: preplanned analysis of OS by histology

**Non-squamous patients**

- **Pemetrexed**
  - Median OS: 15.5 months
- **Placebo**
  - Median OS: 10.3 months
- HR: 0.70

**Squamous patients**

- **Pemetrexed**
  - Median OS: 9.9 months
- **Placebo**
  - Median OS: 10.8 months
- HR: 1.07

**Ciuleanu et al. Lancet 2009; 374: 1432-40.**
## Pemetrexed and NSCLC histology: hazard ratios for overall survival

<table>
<thead>
<tr>
<th>Histology</th>
<th>1st line: Cis-Pem vs Cis-Gem</th>
<th>2nd line: Pem vs Doc</th>
<th>Maintenance: Pem vs Plac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous</td>
<td>0.81*</td>
<td>0.78 *</td>
<td>0.70 *</td>
</tr>
<tr>
<td>Squamous</td>
<td>1.23</td>
<td>1.56 *</td>
<td>1.07</td>
</tr>
</tbody>
</table>

### Conclusion:
- Pemetrexed is superior compared to gemcitabine (and placebo) in patients with non-squamous NSCLC and/or
- Pemetrexed has no anti-tumoral activity in squamous cell NSCLC

Resistance to pemetrexed in cancer cell line is solely due to upregulation of thymidylate synthase (TS)
Thymidylate expression in lung cancer

**FIGURE 1.** Thymidylate synthase messenger RNA levels are illustrated in adenocarcinoma compared with squamous cell carcinoma. Horizontal lines in the middle represent median values, and upper and lower bars represent the distance from the 10th to 90th percentile from the median, respectively.
Thymidylate expression in lung cancer

- The LCC immunoprofile may resemble that of SCCs or ADCs.
- This immunoprofile is associated with differential TS expression levels.

LCC: large cell carcinoma
SCLC: small cell lung cancer

Pemetrexed and NSCLC histology: hazard ratios for overall survival

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</thead>
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<tr>
<td>Non-squamous</td>
<td>0.81*</td>
<td>0.78 *</td>
<td>0.70 *</td>
</tr>
<tr>
<td><strong>Adenocarcinoma</strong></td>
<td><strong>0.84</strong></td>
<td><strong>0.92</strong></td>
<td><strong>0.73</strong></td>
</tr>
<tr>
<td>Large cell</td>
<td>0.67</td>
<td>0.27 *</td>
<td>0.98</td>
</tr>
<tr>
<td>NOS</td>
<td>1.08</td>
<td>0.57</td>
<td>0.61 *</td>
</tr>
<tr>
<td>Squamous</td>
<td>1.23</td>
<td>1.56 *</td>
<td>1.07</td>
</tr>
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  • Gemcitabine
  • Paclitaxel
DNA Damage and DNA repair mechanisms

Cisplatin-based chemotherapy and DNA repair mechanisms

Excision repair cross-complementation group 1 (ERCC1)
- ERCC1 is a rate-limiting protein in the NER and ICL-R pathways, which works by recognising and removing platinum adducts and by repairing interstrand DNA cross-links

Ribonucleotide reductase messenger 1 (RRM1)
- RRM1 is the regulatory component of ribonucleotide reductase, which assists with DNA synthesis and repair.
- RRM1 is the predominant target of the nucleoside analogue gemcitabine.
- RRM1 mediates suppression of cell migration and tumour metastasis by inducing PTEN, a prominent tumour-suppressor gene responsible for attenuation of growth-factor pathway signalling.
Cisplatin-based chemotherapy and DNA repair mechanisms

Breast cancer type 1 susceptibility protein (BRCA1)

- BRCA1 is a component of multiple repair pathways and plays a central role in DNA repair:
  - is involved in the repair of double-strand DNA breaks by the HR and NH-EJ pathways
  - is implicated in the transcription-coupled NER and the ICL-R pathway.
  - is a component of the BRCA1-associated genome surveillance complex, suggesting a role for BRCA1 in mismatch repair
- BRCA1 and β-tubulin co-localise to the microtubules of the mitotic spindle → potential regulator of mitotic spindle assembly.
- BRCA1 has been implicated BRCA1 in apoptosis via the c-Jun N-terminal kinase pathway.

HR: homologous repair   NH-EJ: nonhomologous end joining
NER: nucleoside excision repair
ICL-R: interstrand cross-link repair

### Biomarkers and cisplatin-based chemotherapy in NSCLC

<table>
<thead>
<tr>
<th>Biomarker</th>
<th>Prognostic Significance</th>
<th>Predictive Significance</th>
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<tbody>
<tr>
<td>ERCC1 overexpression</td>
<td>conflicting results</td>
<td>resistance to cisplatin</td>
</tr>
<tr>
<td>RRM1 overexpression</td>
<td>better prognosis</td>
<td>resistance to cisplatin</td>
</tr>
<tr>
<td>BRCA1 overexpression</td>
<td>worse prognosis</td>
<td>resistance to cisplatin sensitivity taxane/vinca</td>
</tr>
</tbody>
</table>

- **Based on surgical series of untreated pts**
- **Based on preclinical data, retrospective analyses, uncontrolled phase 2 trials and IALT**

RRM1 and ERCC1 in Gemcitabine treated NSCLC

Gemcitabine monotherapy

Gemcitabine + Carboplatin

R

N=170

Median OS

<table>
<thead>
<tr>
<th></th>
<th>G</th>
<th>G+C</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>5.1 m</td>
<td>6.7 m</td>
</tr>
</tbody>
</table>

RRM1 (and ERCC1) overexpression is correlated with resistance to gemcitabine (and carboplatin) chemotherapy in NSCLC

Molecular Analysis-Directed Therapy in NSCLC

Trial Eligible (n = 60): NSCLC, stage IIIb/IV, no prior therapy, PS 0-1

- Laser capture microdissection (n = 55)
- Inadequate specimen for LCM (n = 5)
- Real-time RT-PCR (n = 56)
- Patients never started treatment (n = 2)
- Patients started treatment (n = 53)

RR MST 1-yr OS

Individualized chemo 44 % 13.3 m 59%

Fig 3. Overall survival (OS) by assigned chemotherapy. DC, docetaxel and carboplatin; GC, gemcitabine and carboplatin; DV, docetaxel and vinorelbine; GD, gemcitabine and docetaxel.
Customizing Cisplatin-chemotherapy based on ERCC1 mRNA expression in NSCLC

<table>
<thead>
<tr>
<th>Assignment</th>
<th>Control arm</th>
<th>Genotypic arm</th>
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<tbody>
<tr>
<td>ERCC1 levels</td>
<td>Low</td>
<td>High</td>
</tr>
<tr>
<td>Low ERCC1 mRNA</td>
<td>Docetaxel / cisplatin</td>
<td>Docetaxel / cisplatin</td>
</tr>
<tr>
<td>High ERCC1 mRNA</td>
<td>Docetaxel / gemcitabine</td>
<td>Docetaxel / gemcitabine</td>
</tr>
<tr>
<td>RR</td>
<td>PFS</td>
<td>MST</td>
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<tr>
<td>Control arm</td>
<td>40%</td>
<td>5.2 m</td>
</tr>
<tr>
<td>Genotypic arm</td>
<td>51%</td>
<td>6.1 m</td>
</tr>
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</table>

Customizing chemo based on tumor ERCC1 mRNA expression:
• is feasible in the clinical setting
• improves response rate (but not overall survival)
BRCA1 as predictor of survival in patients with resected NSCLC treated with induction cis + gemci

![Graph showing survival probability with different quartiles of BRCA1 mRNA expression.]

Bottom quartile BRCA1 mRNA

Middle quartiles BRCA1 mRNA

Top quartile BRCA1 mRNA

N = 55
BRCA1 has differential modulating effect on chemotherapy

BRCA1 expression induces resistance to cisplatin and sensitivity to paclitaxel and vinorelbine.

Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression

- RNA & DNA extraction from tumor
- $EGFR$ mutation +
  - Erlotinib
- BRCA1 mRNA expression in EGFR WT$^*$
  - Low: Cisplatin + Gemcitabine
  - Intermediate: Cisplatin + Docetaxel
  - High: Docetaxel monotherapy

$^*$ exploratory analysis of RAP80 and Abraxas expression
Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>MST</th>
<th>1y OS</th>
<th>2y OS</th>
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<tbody>
<tr>
<td>EGFR mut +</td>
<td>12</td>
<td>NR</td>
<td>92%</td>
<td>73%</td>
</tr>
<tr>
<td>BRCA1 low</td>
<td>38</td>
<td>11m</td>
<td>48%</td>
<td>41%</td>
</tr>
<tr>
<td>BRCA1 inter</td>
<td>40</td>
<td>9m</td>
<td>41%</td>
<td>16%</td>
</tr>
<tr>
<td>BRCA1 high</td>
<td>33</td>
<td>11m</td>
<td>42%</td>
<td>0%</td>
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</table>

Bringing BRCA1 to Sites of DNA Damage

- Histone γ-H2AX and MDC1 are recruited to site of DNA damage
- Ubiquilation of γ-H2AX and MDC1 complex occurs
- RAP80 (and Abraxas) are attracted to the site
- RAP80 transfers BRCA1 to the site of DNA-damage

MDC1: mediator of DNA-damage checkpoint 1
BRCA1: breast cancer susceptibility gene 1
RAP80: receptor associated protein 80
RAP80 and DNA repair mechanisms

Receptor associated protein 80 (RAP80):

• acts upstream of BRCA1

• is required for accumulation of BRCA1 to sites of double strand DNA breaks
  → RAP80 is required for DNA damage repair

• is able to translocate to DNA-damage foci in cells which express a truncated BRCA1 that is unable to migrate to nuclear foci
  → RAP 80 could replace the BRCA1 DNA repair function in cells lacking BRCA1
Customized treatment of NSCLC based on EGFR mutations and BRCA1 mRNA expression

Median survival ~ BRCA1 and RAP80 expression

<table>
<thead>
<tr>
<th>BRCA1 mRNA</th>
<th>Low</th>
<th>Intermediate</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>NR</td>
<td>8 m</td>
<td>7 m</td>
</tr>
<tr>
<td>Intermediate</td>
<td>5 m</td>
<td>13 m</td>
<td>16 m</td>
</tr>
<tr>
<td>High</td>
<td>6 m</td>
<td>12 m</td>
<td>11 m</td>
</tr>
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</table>

Cisplatin + Gemcitabine
Cisplatin + Docetaxel
Docetaxel monotherapy

BREC trial: design

**Treatment naïve advanced NSCLC**

**CONTROL**

- 1:1

**EXPERIMENTAL**

- T1 RAP80 (T1-T3 BRCA1) → Gem/Cis
- T2-T3 RAP80 (T1-T2 BRCA1) → Docetaxel/Cis
- T2-T3 RAP80 (T3 BRCA1) → Docetaxel

**Docetaxel/Cis**

Sample size: 480

**Primary endpoint:**
- Time to progression between the standard non-customized first-line chemotherapy group and the 3 customized chemotherapy subgroups
## Selection factors for customizing systemic treatment for NSCLC

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Selection factor</th>
<th>Effect</th>
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<tbody>
<tr>
<td>Tumor histology</td>
<td>EGFR-TKI</td>
<td>Adeno</td>
<td>Improved response rate</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>Non-Squamous</td>
<td>Exclusion non-benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Non-Squamous</td>
<td>Safety</td>
</tr>
<tr>
<td>Molecular tumor biomarkers</td>
<td>EGFR-TKI</td>
<td>EGFR-mutation</td>
<td>Improved PFS</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>Low TS expression</td>
<td>Selection benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Low RRM1</td>
<td>Selection benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Platinum</td>
<td>ERCC1, BRCA1 or</td>
<td>Improved RR, PFS and/or OS</td>
</tr>
<tr>
<td></td>
<td></td>
<td>RAP80 expression</td>
<td></td>
</tr>
</tbody>
</table>

Data from adequately powered RCTs with prospective biomarker analysis
Personalized treatment in NSCLC

• Aims and challenges of biomarker driven treatment
• Treatment customized on histology or tumor biomarkers
  - Targeted therapies:
    • EGFR-TKIs
    • Anti-VEGF
  - Chemotherapy:
    • Pemetrexed
    • Cisplatin-based chemotherapy
• Treatment customized on patient genotype markers
  • Gemcitabine
  • Paclitaxel
Correlation of CDA Polymorphisms with Outcome in Gemcitabine/Cisplatin Treated NSCLC

- The metabolic inactivation of gemcitabine is catalyzed by cytidine deaminase (CDA).
- *CDA* polymorphisms were analyzed in 65 chemonaive NSCLC pts treated with cisplatin + gemcitabine:
  - mean enzymatic activity in carriers of Lys/Gln and Gln/Gln genotypes was 1.7-fold higher compared to the wild-type CDA<sup>27</sup> Lys/Lys (P = 0.048)

<table>
<thead>
<tr>
<th>CDA Lys&lt;sup&gt;27&lt;/sup&gt;Gln</th>
<th>Incidence</th>
<th>RR</th>
<th>MST</th>
<th>Gr 3-4 Neutropenia</th>
<th>Gr 3-4 Thrombopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lys/Lys</td>
<td>38%</td>
<td>52%</td>
<td>17 m</td>
<td>48%</td>
<td>33%</td>
</tr>
<tr>
<td>Lys/Gln</td>
<td>47%</td>
<td>31%</td>
<td>14 m</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Gln/Gln</td>
<td>15%</td>
<td>11%</td>
<td>4 m</td>
<td>22%</td>
<td>11%</td>
</tr>
</tbody>
</table>

Cytidine deaminase (CDA) activity in serum and severe toxicities with gemcitabine

- Gemcitabine is primarily detoxified by cytidine deaminase

A. Gemcitabine monotherapy
B. Gemcitabine combinations

→ CDA deficiency is associated with a maximum risk of developing early severe toxicities with gemcitabine
Pharmacogenomic analysis of the common carboplatin-paclitaxel arm in US-Japanese trials

- Genomic DNA was prospectively collected in three phase III trials in advanced NSCLC, each with a common arm of paclitaxel plus carboplatin.
- Population-based pharmacogenomic analysis of genotypic variants of CYP3A4, CYP3A5, CYP2C8, NR1I2-206, ABCB1, ERCC1, and ERCC2 was performed.
- The CYP3A isozymes account for 45% to 60% of paclitaxel metabolism.
- An association was observed between occurrence of the CYP3A4*1B allele and PFS (P = .04)
  (this association should be interpreted in the context that only African American patients harbored this allele)
### Selection factors for customizing systemic treatment for NSCLC

<table>
<thead>
<tr>
<th>Category</th>
<th>Drug</th>
<th>Selection factor</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tumor histology</strong></td>
<td>EGFR-TKI</td>
<td>Adeno</td>
<td>Improved response rate</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>Non-Squamous</td>
<td>Exclusion non-benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Non-Squamous</td>
<td>Safety concerns in squamous</td>
</tr>
<tr>
<td><strong>Molecular tumor biomarkers</strong></td>
<td>EGFR-TKI</td>
<td>EGFR-mutation</td>
<td>Improved PFS</td>
</tr>
<tr>
<td></td>
<td>Pemetrexed</td>
<td>Low TS expression</td>
<td>Selection of benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Gemcitabine</td>
<td>Low RRM1</td>
<td>Selection of benefiting pts</td>
</tr>
<tr>
<td></td>
<td>Platinum</td>
<td>ERCC1, BRCA1, RAP80</td>
<td>Improved RR, PFS and/or OS</td>
</tr>
<tr>
<td><strong>Patient genotype</strong></td>
<td>Gemcitabine</td>
<td>CDA 27 Lys/Lys</td>
<td>Improved OS(worse toxicity)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>CYP3A4 SNP</td>
<td>Improved PFS</td>
</tr>
</tbody>
</table>

Data from adequately powered RCTs with prospective biomarker analysis
Personalized treatment of NSCLC

“The future is now

“NSCLC is a common cancer”

“NSCLC is a collection of rare cancers”