Personalized treatment in NSCLC: fact or fiction?

Paul Germonpré

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
- TNM-stage
- Performance status
- Age and comorbidities
- Toxicties
- Treatment administration
- Experience with drug

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

Personalized treatment in NSCLC
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  - Anti-VEGF
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  - Cisplatin-based chemotherapy
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  - Gemcitabine
  - Paclitaxel

Development of Personalized Therapy for NSCLC

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

- Hypothesis testing
  - Retrospective analysis
  - Non-stratified

- Double-blind randomized
  - Placebo-controlled
  - Adequately powered

- Prospective analysis
  - Stratified by biomarker status

Switching to personalized treatment

- Tumor characteristics
  - TNM-stage
  - Tumor biomarkers

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

- Patient preference
  - Toxocities
  - Treatment administration

- Doctor preference
  - Experience with drug

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
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  - Paclitaxel

Signal Transduction Pathways Controlled by the Activation of EGFR

BR.21: predictors of response

<table>
<thead>
<tr>
<th>Ethanol Patients (%)</th>
<th>n=427</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female (146)</td>
<td>14.4</td>
<td>0.006</td>
</tr>
<tr>
<td>Male (281)</td>
<td>6.1</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (209)</td>
<td>13.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Other (218)</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (63)</td>
<td>18.9</td>
<td></td>
</tr>
<tr>
<td>Other (374)</td>
<td>7.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Ever smoked</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (211)</td>
<td>3.8</td>
<td></td>
</tr>
<tr>
<td>No (205)</td>
<td>24.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Unknown (33)</td>
<td>15.9</td>
<td></td>
</tr>
</tbody>
</table>

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>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (475)</td>
<td>0.8</td>
<td>0.6–0.9</td>
<td>0.76</td>
</tr>
<tr>
<td>Female (256)</td>
<td>0.8</td>
<td>0.6–1.1</td>
<td></td>
</tr>
<tr>
<td>Histology</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adenocarcinoma (265)</td>
<td>0.7</td>
<td>0.6–2.9</td>
<td>0.37</td>
</tr>
<tr>
<td>Other (266)</td>
<td>0.8</td>
<td>0.6–1.0</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian (91)</td>
<td>0.6</td>
<td>0.4–1.0</td>
<td>0.44</td>
</tr>
<tr>
<td>Other (460)</td>
<td>0.8</td>
<td>0.7–2.9</td>
<td></td>
</tr>
<tr>
<td>Smoking History</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever (545)</td>
<td>0.9</td>
<td>0.7–1.0</td>
<td></td>
</tr>
<tr>
<td>Never (146)</td>
<td>0.4</td>
<td>0.3–4.6</td>
<td>0.02</td>
</tr>
<tr>
<td>Unknown (40)</td>
<td>1.1</td>
<td>0.5–2.6</td>
<td></td>
</tr>
</tbody>
</table>

*Significance between subgroups

* p-value for interaction between ethanol and clinical variables
Effect of Deletions and Mutations in EGFR on Disease Development and Drug Targeting

- Constitutively active TK (ligand independent)
- 80% of EGFR mutations; results in constitutive EGFR activation
- Associated with acquired resistance to EGFR-TKI

IPASS: Progression-free survival

<table>
<thead>
<tr>
<th>EGFR-mutation positive</th>
<th>EGFR-mutation negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gefitinib</td>
<td>Carbo/Paclitaxel</td>
</tr>
<tr>
<td>Response rate</td>
<td></td>
</tr>
<tr>
<td>71%</td>
<td>47%</td>
</tr>
<tr>
<td>Median PFS</td>
<td></td>
</tr>
<tr>
<td>9.6 m</td>
<td>6.3 m</td>
</tr>
</tbody>
</table>

IPASS: Overall survival

- 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

WJTOG3405: 1st line gefitinib vs chemotherapy

Inclusion criteria:
- Chemoradiation pts
- EGFR activating mutation

Statistics: PFS as primary endpoint

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
EGFR mutations identify patients who derive a great PFS-benefit from erlotinib maintenance (median PFS 45 wks vs 13 wks).

Signal Transduction Pathways Controlled by the Activation of EGFR

ALK gene rearrangements and crizotinib in NSCLC
- ALK gene rearrangements:
  - occur in 3-5% of unselected NSCLC
  - higher frequency in adenocarcinoma 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

NSCLC: driver mutations
- Genetic alterations responsible for initiating and maintaining lung cancer:
  - Squam.Ca
  - AdenoCA
  - Large cell CA
- EGFR mutations (10-40%)
- KRAS mutations (10-30%)
- EML4-ALK fusion (~10%)
- other

Bevacizumab and NSCLC
- Randomized phase 2 trial of carbo-paclitaxel ± 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.
**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: Cisplatin, Pemetrexed, Cisplatin-based chemotherapy
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**Cisplatin+Pemetrexed vs Cisplatin+Gemcitabine in 1st-line treatment of advanced NSCLC**

- Inclusion criteria:
  - Chem-naive advanced NSCLC
  - PS 0-2
  - No CNS metastasis
- Every 3 weeks for 4 cycles

**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>

**Maintenance arm:**

- Cis-Pem arm *
  - Cisplatin 75 mg/m² q2wks
  - Pemetrexed 500 mg/m² q2wks

- Cis-Gem arm *
  - Cisplatin 75 mg/m² q2wks
  - Gemcitabine 1250 mg/m² q2wks

---

**Pemetrexed as maintenance in 1st-line treatment of advanced NSCLC**

- Inclusion criteria:
  - PS 0-1
  - Non-progressing following 4 cycles of platinum + gemcitabine or paclitaxel

**ITT population**

<table>
<thead>
<tr>
<th></th>
<th>Pemetrexed</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (m)</td>
<td>15.5</td>
<td>10.3</td>
</tr>
</tbody>
</table>

**Maintenance arm:**

- Pemetrexed 500 mg/m² q2wks until PD (n=441)

**Control arm:**

- Placebo q2wks until PD (n=229)

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**Pemetrexed maintenance trial: preplanned analysis of OS by histology**

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous patients</th>
<th>Squamous patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>15.5</td>
<td>10.3</td>
</tr>
<tr>
<td>Pemetrexed</td>
<td>9.9</td>
<td>10.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Non-squamous patients</th>
<th>Squamous patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS (months)</td>
<td>0.81</td>
<td>0.78</td>
</tr>
</tbody>
</table>

**Histology**

- 1st line: Cis-Pem vs Cis-Gem
- 2nd line: Pem vs Doc
- Maintenance: Pem vs Plac

**Histology**

- Non-squamous: 0.81
- Squamous: 1.23

**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.
Pemetrexed: mechanism of action

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

Thymidylate expression in lung cancer

- TS mRNA expression
- TS protein expression

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

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>Adenocarcinoma</td>
<td>0.84*</td>
<td>0.92</td>
<td>0.73*</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>
</tbody>
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Personalized treatment in NSCLC

- Aims and challenges of biomarker driven treatment
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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.

Biomarkers and cisplatin-based chemotherapy in NSCLC

<table>
<thead>
<tr>
<th>Prognostic significance</th>
<th>Predictive significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>ERCC1 overexpression</td>
<td>confounding results</td>
</tr>
<tr>
<td>RRM1 overexpression</td>
<td>better prognosis</td>
</tr>
<tr>
<td>BRCA1 overexpression</td>
<td>worse prognosis</td>
</tr>
</tbody>
</table>

Based on surgical series of untreated pts

RRM1 and ERCC1 in Gemcitabine treated NSCLC

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

Molecular Analysis-Directed Therapy in NSCLC

<table>
<thead>
<tr>
<th>RR</th>
<th>MST</th>
<th>1-yr OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>44%</td>
<td>13.3 m</td>
<td>59%</td>
</tr>
</tbody>
</table>

Customizing Cisplatin-chemotherapy based on ERCC1 mRNA expression in NSCLC

Control arm: 40% RR, 5.2 m MST, 39% 1-yr OS, 39% 2-yr OS
Genotypic arm: 51% RR, 6.1 m MST, 41% 1-yr OS, 41% 2-yr OS

Control arm: 40% RR, 5.2 m MST, 39% 1-yr OS, 39% 2-yr OS
Genotypic arm: 51% RR, 6.1 m MST, 41% 1-yr OS, 41% 2-yr OS

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

- Bottom quartile BRCA1 mRNA
- Middle quartiles BRCA1 mRNA
- Top quartile BRCA1 mRNA

**BRCA1 has differential modulating effect on chemotherapy**

<table>
<thead>
<tr>
<th>Chemotherapy</th>
<th>BRCA1 -</th>
<th>BRCA1 +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>IC50 4.1µM</td>
<td>IC50 2.2µM</td>
</tr>
<tr>
<td>Etoposide</td>
<td>IC50 &gt;100µM</td>
<td>IC50 6.2µM</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>VRB 17µM</td>
<td>VRB 7.2µM</td>
</tr>
<tr>
<td>Vinorelbine</td>
<td>VRB 17µM</td>
<td>VRB 1.9µM</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>EGFR mutation</th>
<th>BRCA1 mRNA expression</th>
<th>Erlotinib</th>
<th>Cisplatin + Gemcitabine</th>
<th>Docetaxel</th>
<th>Cisplatin + Gemcitabine + Docetaxel</th>
<th>Erlotinib + Docetaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR WT</td>
<td>Low</td>
<td></td>
<td>Cisplatin + Gemcitabine</td>
<td>Docetaxel</td>
<td>Docetaxel monotherapy</td>
<td>Erlotinib + Docetaxel</td>
</tr>
<tr>
<td></td>
<td>Intermediate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>High</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>EGFR mut</th>
<th>N</th>
<th>MST</th>
<th>1y OS</th>
<th>2y OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</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>46%</td>
<td>41%</td>
</tr>
<tr>
<td>BRCA1 int</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>
</tr>
</tbody>
</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

**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

<table>
<thead>
<tr>
<th>BRCA1 mRNA</th>
<th>RAP80 mRNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>Low</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Intermediate</td>
</tr>
<tr>
<td>High</td>
<td>High</td>
</tr>
</tbody>
</table>

Median survival ~ BRCA1 and RAP80 expression

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>
</tr>
</thead>
<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>Platinum</td>
<td>ERCC1, BRCA1 or RAP80 expression</td>
<td>Improved RR, PFS and/or OS</td>
<td></td>
</tr>
</tbody>
</table>

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 27 Lys/Lys (P = 0.048)

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

- Gemcitabine is primarily detoxified by cytidine deaminase

→ 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).

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</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>Non-Squamous</td>
<td>Safety concerns in squamous</td>
</tr>
<tr>
<td>Molecular tumor biomarkers</td>
<td>EGFR-TKI</td>
<td>EGFR-mutation</td>
<td>Improved PFS</td>
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<td>Pemetrexed</td>
<td>Low TS expression</td>
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<tr>
<td></td>
<td>Platinum</td>
<td>ERCC1, BRCA1, RAP80</td>
<td>Improved RR, PFS and/or OS</td>
</tr>
<tr>
<td>Patient genotype</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

“NSCLC is a common cancer”

“The future is now”

“NSCLC is a collection of rare cancers”