Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT) 2: Randomized Study of Biomarker-Based Treatment

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THE UNIVERSITY OF TEXAS MD Anderson Cancer Center
Precision Medicine

A form of medicine that uses information about a person’s genes, proteins, and environment to prevent, diagnose, and treat disease

*NCI, 2011*

*Personalized Medicine in Cancer Requires:*
1. Identification of genetic alterations that drive carcinogenesis
2. Development of drugs that can effectively inhibit the function of the genetic alterations

Molecularly targeted therapy to be used consistently and successfully in patients with cancer.
Precision Medicine in a Phase I Program

Initiative for Molecular Profiling in Advanced Cancer Therapy (IMPACT)
Background

• Imatinib: first FDA-approved tyrosine kinase inhibitor (CML): 2002
  Druker et al NEJM 2001;344:1031

• BATTLE (Biomarker-Integrated Approaches of Targeted Therapy for Lung Cancer Elimination)
  Kim ES, Hong WK et al Cancer Discovery 2011;1:42

IMPACT Hypothesis, 2007

• Genetic and molecular analyses of patients’ cancers will enable selection of optimal therapy for each patient
  Tsimberidou et al, Clin Cancer Res. 2012; 18(22):6373-83
<table>
<thead>
<tr>
<th></th>
<th>No. of pts.</th>
<th>% *</th>
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<tbody>
<tr>
<td>Molecular analysis ordered</td>
<td>3,745</td>
<td></td>
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<tr>
<td>Adequate tissue available</td>
<td>3,536</td>
<td>94.4</td>
</tr>
<tr>
<td>No. of aberrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1,447</td>
<td>40.9</td>
</tr>
<tr>
<td>1</td>
<td>1,242</td>
<td>35.1</td>
</tr>
<tr>
<td>2</td>
<td>488</td>
<td>13.8</td>
</tr>
<tr>
<td>≥3</td>
<td>359</td>
<td>10.2</td>
</tr>
<tr>
<td>No. of pts. with aberration</td>
<td>2,089</td>
<td>59</td>
</tr>
</tbody>
</table>

* Proportion was calculated for patients whose tissue was analyzed for ≥ 1 molecular aberration
Molecular Aberrations by Tumor Type (N=3,536)

- Melanoma: 72% (207/289)
- Breast: 71% (240/336)
- Ovarian: 69% (198/285)
- Endometrial: 68% (69/101)
- CRC: 68% (414/606)
- Pancreatic: 65% (53/81)
- GYN other: 54% (115/181)
- Thyroid: 59% (63/106)
- Lung: 58% (164/285)
- GI other: 53% (177/331)
- Head and Neck: 44% (123/277)
- Sarcoma: 42% (77/185)
- GU: 41% (56/136)
- Other: 40% (113/281)
- Renal: 36% (20/56)
### Proportions of Molecular Aberrations (N=3,536)

<table>
<thead>
<tr>
<th>Gene</th>
<th>Proportion</th>
<th>Count (N/Denominator)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER</td>
<td>36.8%</td>
<td>536/1455</td>
</tr>
<tr>
<td>PR</td>
<td>17.6%</td>
<td>480/2728</td>
</tr>
<tr>
<td>TP53</td>
<td>15.7%</td>
<td>177/1124</td>
</tr>
<tr>
<td>KRAS</td>
<td>10.2%</td>
<td>280/2747</td>
</tr>
<tr>
<td>PTEN</td>
<td>7.3%</td>
<td>192/2639</td>
</tr>
<tr>
<td>PIK3CA</td>
<td>5.1%</td>
<td>58/1127</td>
</tr>
<tr>
<td>BRAF</td>
<td>4.8%</td>
<td>99/2047</td>
</tr>
<tr>
<td>HER2</td>
<td>4.4%</td>
<td>74/1682</td>
</tr>
<tr>
<td>NRAS</td>
<td>4.1%</td>
<td>94/2301</td>
</tr>
<tr>
<td>MET</td>
<td>1.3%</td>
<td>26/1942</td>
</tr>
<tr>
<td>EGFR</td>
<td>1.2%</td>
<td>18/1443</td>
</tr>
<tr>
<td>CKIT</td>
<td>0.5%</td>
<td>6/1158</td>
</tr>
<tr>
<td>AKT</td>
<td>0.2%</td>
<td>2/1154</td>
</tr>
</tbody>
</table>

Includes tests performed in ≥ 30 patients
RET mutations: were tested mostly in patients with medullary thyroid cancer
IMPACT 1 (N=3,536): Best Response (RECIST) in Pts. with 1 Molecular Alteration (n=688)

<table>
<thead>
<tr>
<th></th>
<th>Matched TT</th>
<th>Non-Matched</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evaluatable</td>
<td>342</td>
<td>305</td>
<td></td>
</tr>
<tr>
<td>CR+PR (%)</td>
<td>72 (21)</td>
<td>17 (6)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>CR+PR+SD≥6 months (%)</td>
<td>143 (42)</td>
<td>58 (19)</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
IMPACT 1: Pts. with 1 Molecular Alteration (n=688)

Progression-Free Survival

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>Matched TT</th>
<th>Non-Matched</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>358</td>
<td>330</td>
<td></td>
</tr>
<tr>
<td>Median PFS, months</td>
<td>4.1</td>
<td>2.4</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Median OS, months</td>
<td>10.2</td>
<td>8.2</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
## Multivariate Analysis for Response Treated Patients with 1 Aberration (N=607)

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR*</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched therapy (vs. non-matched)</td>
<td>3.12</td>
<td>2.12-4.61</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No Liver Metastases</td>
<td>2.10</td>
<td>1.35-3.27</td>
<td>.001</td>
</tr>
<tr>
<td>Albumin ≥ ULN (vs. &lt; ULN)</td>
<td>3.91</td>
<td>1.50-10.19</td>
<td>.005</td>
</tr>
<tr>
<td>LDH ≤ ULN (vs. &gt; ULN)</td>
<td>1.54</td>
<td>0.99-2.38</td>
<td>.052</td>
</tr>
</tbody>
</table>

* OR = Odds Ratio (>1 is associated with higher response)
# Multivariate Analysis for TTF Treated Patients with 1 Aberration

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR *</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Matched therapy (vs. non-matched)</td>
<td>.56</td>
<td>.47-.66</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Albumin ≥ 3.5 g/dL (vs. &lt; 3.5 g/dL)</td>
<td>.42</td>
<td>.32-.56</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>No liver metastases (vs. liver mets)</td>
<td>.68</td>
<td>.57-.81</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>LDH ≤ ULN (vs. &gt; ULN)</td>
<td>.75</td>
<td>.63-.90</td>
<td>.002</td>
</tr>
<tr>
<td>Performance status &lt;2</td>
<td>.81</td>
<td>.67-.98</td>
<td>.030</td>
</tr>
</tbody>
</table>

* HR = Hazard Ratio (<1 is associated with longer TTF)
## Clinical Outcomes by No. of Aberrations and Type of Therapy (Non-Randomized)

<table>
<thead>
<tr>
<th>No. of Aberr.</th>
<th>Therapy</th>
<th>N</th>
<th>CR+PR+ SD≥6 Mo. (%)</th>
<th>P</th>
<th>TTF, Mo.</th>
<th>P</th>
<th>OS, Mo.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Matched</td>
<td>306</td>
<td>113/293 (39)</td>
<td>&lt;.0001</td>
<td>4.0</td>
<td>&lt;.0001</td>
<td>11.2</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>Not matched</td>
<td>360</td>
<td>52/337 (15)</td>
<td>2.0</td>
<td></td>
<td></td>
<td>8.6</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Matched</td>
<td>101</td>
<td>21/82 (26)</td>
<td>.30</td>
<td>3.1</td>
<td>0.19</td>
<td>9.9</td>
<td>.31</td>
</tr>
<tr>
<td></td>
<td>Not matched</td>
<td>68</td>
<td>10/57 (18)</td>
<td>2.3</td>
<td></td>
<td></td>
<td>6.6</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>Matched</td>
<td>33</td>
<td>9/26 (35)</td>
<td>.71</td>
<td>3.2</td>
<td>.04</td>
<td>7.7</td>
<td>.63</td>
</tr>
<tr>
<td></td>
<td>Not matched</td>
<td>14</td>
<td>3/12 (25)</td>
<td>1.6</td>
<td></td>
<td></td>
<td>7.8</td>
<td></td>
</tr>
</tbody>
</table>
### Patients with 1 Aberration. Response by Type of Therapy and BRAF Mutational Status

<table>
<thead>
<tr>
<th>Aberration</th>
<th>Type of Therapy</th>
<th>No. of treated pts.</th>
<th>CR/PR (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF Matched</td>
<td>Matched</td>
<td>98</td>
<td>32 (33)</td>
<td>.0009</td>
</tr>
<tr>
<td></td>
<td>Non-matched</td>
<td>20</td>
<td>0 (0)</td>
<td></td>
</tr>
<tr>
<td>Non-BRAF Matched</td>
<td>Matched</td>
<td>195</td>
<td>24 (12)</td>
<td>.0007</td>
</tr>
<tr>
<td></td>
<td>Non-matched</td>
<td>317</td>
<td>14 (4)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>Matched</td>
<td>293</td>
<td>56 (19)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td></td>
<td>Non-matched</td>
<td>337</td>
<td>14 (4)</td>
<td></td>
</tr>
</tbody>
</table>
2-Month Landmark Analysis: PFS

Matched Therapy

Non-Matched Therapy

Tsimberidou et al, Clin Cancer Res. 2014; 20(18):1-10
2-Month Landmark Analysis: Survival

Matched Therapy

Non-Matched Therapy

Tsimberidou et al, Clin Cancer Res. 2014; 20(18):1-10
Salivary Cancer With BRAF Mutation V600E Treated With Vemurafenib
Major Shift in War on Cancer

• The MD Anderson program pooled 1,144 patients in a phase I study after profiling their tumors for mutations that might be targets of the tested drugs.

• Apostolia Tsimberidou, the researcher who led the study, reported that 40% had mutations in 10 molecular pathways that were targeted by the experimental compounds.

• Tumors in 27% of those given agents that targeted their mutations responded to treatment compared to 5% for those with unmatched therapies.
Taking aim sooner

If personalized medicine is to achieve its full potential, it should be used earlier on in clinical trials.

Many scientists … believe that matching volunteers' genetic profiles to the drugs being tested will not only be better for the volunteers, but may also speed up the trials, and save millions of dollars in the process. One such is Apostolia-Maria Tsimberidou of the University of Texas's MD Anderson Cancer Centre, in Houston. And her preliminary results, presented this week at a meeting of the American Society of Clinical Oncology in Chicago, suggest she is right.
Ongoing Challenges in Implementation of Precision Medicine
## Challenges: Current Barriers

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biopsy for molecular profile</td>
<td>Not standard</td>
<td>Standard of care</td>
</tr>
<tr>
<td>CLIA, comprehensive test</td>
<td>Not standard</td>
<td>Standard of care</td>
</tr>
<tr>
<td>Bioinformatics</td>
<td>Limited</td>
<td>Optimized</td>
</tr>
<tr>
<td>Molecular analysis, results</td>
<td>10-60 days</td>
<td>1-3 days</td>
</tr>
<tr>
<td>Clinical trial/targeted agent</td>
<td>≈10-30% of patients</td>
<td>100% of patients</td>
</tr>
<tr>
<td>Selection of targeted therapy</td>
<td>Subjective</td>
<td>Evidence-based</td>
</tr>
<tr>
<td>Adaptive learning, “N of 1”</td>
<td>&lt;10%</td>
<td>100%</td>
</tr>
</tbody>
</table>
Challenges: Molecular Profiling

- Implementation of technology
- Biopsy: timing, cost, selection of metastatic sites, tumor periphery vs. center, most easily accessible
- Tissue quality, % tumor cells
- Centralized pathology review
- Complete molecular profile platform, CLIA, ESO
- Bioinformatics: driver vs. passenger alteration
- Identification of new targets
Challenges: Molecularly Targeted Therapy

Selection of optimal treatment
- Decision support tools, clinical trial design, tumor board
- Functional testing for aberration + drug

Prevention of resistance to targeted therapy
- Combinations of molecularly targeted agents
- Targeting multiple driver aberrations, sequential vs. simultaneous
- Off & on target inhibition
- Combination with chemotherapy
- Early eradication of significant subclone
- Frequent tumor biopsies to monitor target inhibition and emergence of new aberrations
65% mutations from a single biopsy are heterogeneous – not shared by all parts of the tumour.

Gerlinger et al. NEJM, 2012:366,883

Courtesy of Dr. Andrew Futreal
Intra-Patient Heterogeneity May Foster Tumor Adaptation and Therapeutic Failure

### Longitudinal Evaluation of Patients Treated Repeatedly with Erlotinib

#### A

<table>
<thead>
<tr>
<th>Histology</th>
<th>Genotype</th>
<th>EGFR TKI status</th>
<th>Tumor burden</th>
<th>Treatment</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno</td>
<td>L858R</td>
<td>Sensitive</td>
<td></td>
<td>Chemo</td>
<td>2007</td>
</tr>
<tr>
<td>Adeno</td>
<td>L858R</td>
<td>Resistant</td>
<td></td>
<td>Erlotinib</td>
<td>2008</td>
</tr>
<tr>
<td>Adeno</td>
<td>L858R</td>
<td>Sensitive</td>
<td></td>
<td>Chemo</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>TP53</td>
<td></td>
<td></td>
<td>Erlotinib</td>
<td>2010</td>
</tr>
<tr>
<td></td>
<td>T790M</td>
<td></td>
<td></td>
<td></td>
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</table>

#### B

<table>
<thead>
<tr>
<th>Histology</th>
<th>Genotype</th>
<th>EGFR TKI status</th>
<th>Tumor burden</th>
<th>Treatment</th>
<th>Timeline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adeno</td>
<td>L858R</td>
<td>Sensitive</td>
<td></td>
<td>Erlotinib</td>
<td>2008</td>
</tr>
<tr>
<td>SCLC</td>
<td>L858R</td>
<td>Resistant</td>
<td></td>
<td>C+RT</td>
<td>2009</td>
</tr>
<tr>
<td>Adeno</td>
<td>L858R</td>
<td>Sensitive</td>
<td></td>
<td>Erlotinib</td>
<td>2010</td>
</tr>
<tr>
<td>SCLC</td>
<td>PIK3CA</td>
<td>Resistant</td>
<td></td>
<td>C+ RT</td>
<td></td>
</tr>
</tbody>
</table>

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Molecular Diagnostics and Point of Care Testing. A Key Future Driver in the Healthcare Value Chain

Complex biosignature profiling

<table>
<thead>
<tr>
<th>Genomics</th>
<th>Proteomics</th>
<th>Immunosignatures</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Genomics Image" /></td>
<td><img src="image2" alt="Proteomics Image" /></td>
<td><img src="image3" alt="Immunosignatures Image" /></td>
</tr>
</tbody>
</table>

Signature detection, deconvolution and multivariate analysis

- Automated, high throughput multiplex assays
- Novel test formats and devices (POC)
- New algorithms for complex signal/deconvolution
Ethnic Diversity in Drug Effects

Anticancer Drugs

Worldwide Cancer Patients

Environmental differences
Local practice differences
Drug-drug interaction differences
Genetic differences

PHARMACOETHNICITY
Ethnic diversity in drug response or toxicity

Intratumour Heterogeneity and Predicting Outcome: Myeloma subclone determining final outcome: <1% of population

Challenges of Cancer Evolution and Heterogeneity

Tumor Heterogeneity Supports Evolutionary Fitness
- Progression to invasive carcinoma
- Poor Clinical Outcome

Tumor Adaptation and Selection for
- Drug resistance
- Metastatic growth

Tumor Sampling Bias
- Different tumor biopsies, different results
- Sites of disease evolve independently

Consider Clonal Dominance of Actionable Mutations
- Mutations present at one site but not another
Intra-tumor Heterogeneity: How to Resolve it?

Circulating free tumor DNA

LETTER

Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA

Muhammed Murtaza¹*, Sarah-Jane Dawson¹,²*, Dana W. Y. Tsui¹*, Davina Gale¹, Tim Forshey¹, Anna M. Piskorz¹, Christine Parkinson¹,², Suet-Feung Chin¹, Zoya Kingsbury³, Alvin S. C. Wong⁴, Francesco Marass³, Sean Humphray³, James Hadfield¹, David Bentley³, Tan Min Chin⁴,⁵, James D. Brenton¹,²,⁶, Carlos Caldas¹,²,⁶ & Nitzan Rosenfeld¹
APOLLO is enabled by adaptive learning

Clinical information and data

Patient Consent, Biospecimen Collection, QC, Banking, Biomolecule Processing

Omics & Research Data

Big Data Warehouse

Big Data Analytics

Insight discovery
Clinical decision support
Business Analytics

Research

Dr. Andrew Futreal
CancerLinQ
A continuous cycle of learning

Richard L. Schilsky. ASCO 2013
IMPACT 2 Study: Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer
Precision Medicine: Role of Prospective Studies

Precision medicine → Encouraging results

Challenge: Not well-validated
Solution: Prospective randomized controlled trials

Challenge: Multiple new tests; too few patients to analyze
Solution: Innovative study designs

Objective: To assess the effectiveness of molecular profiling to select targeted therapy

Tsimberidou et al. ASCO Educational Book 2014: 61-9
Randomized Study Evaluating Molecular Profiling and Targeted Agents in Metastatic Cancer (IMPACT 2)

Primary Objective

To determine whether patients treated with a targeted therapy selected on the basis of mutational analysis of the tumor have longer PFS from the time of randomization than those whose treatment is not selected based on alteration analysis

PI: Tsimberidou, AM; Co-PIs: Berry, D; Meric-Bernstam, F
NCT02152254
Supported by a research grant from Foundation Medicine
IMPACT 2. Study Design (I)

Metastatic disease (0-3 prior therapies)

Tumor biopsy for molecular profiling, 100%

If patient can’t wait for results of MP (with up to 2 prior therapies), they may receive 1 line of therapy, excluding targeted therapy

Targetable molecular aberrations (≥1 aberration)

Yes, 50% (n≈613)  No, 50% (n≈613)

FDA-approved drugs within labeled indication

Yes, 30% (n≈184)  No, 70% (n≈429)

Excluded; patient followed for progression but not randomized

Is there a clinical trial or commercially available targeted therapy?

→ Yes, 70% (n≈300)  Randomize
Targeted therapy*
If:
- Progressive disease
- Toxicity

Treatment not selected based on molecular analysis

Crossover

* Expansion phase of phase I studies or phase II studies
Key Inclusion Criteria

1. Metastatic cancer who have had up to three prior treatments (excluding biologics, cytokines or cell therapies).
2. Pathologically confirmed cancer by tumor biopsy and/or fine-needle aspiration.
3. Measurable disease
4. ECOG performance status 0-1
5. The patient has biopsy-accessible tumor.
6. Normal organ function
7. Age $\geq 18$ years
Key Exclusion Criteria

1. The patient has received chemotherapy, surgery, or radiotherapy within 3 weeks of initiating study treatment (4 weeks for bevacizumab or investigational drugs) or the patient has not recovered (Grade $\leq 1$) from side effects of the previous therapy (localized palliative radiotherapy within 2 weeks is allowed).

2. Patients to be randomized: Patients for whom an FDA-approved therapy for the tumor type and the molecular aberration is available will be excluded from the randomization.

3. Surgery within 30 days of study entry, excluding diagnostic biopsy.
Tumor Board

- To establish: ordered list of alterations & ordered list of trials/drugs
- Order: may depend on organ site
- Each individual Department will determine: trial priority per tumor type & will provide updated lists
- Meeting/Teleconference: every 2 wks
- Protocol master database: weekly updates
- Development of a treatment algorithm
IMPACT2: Treatment Assignment

An ordered list of possible drugs by alterations and organ site will be established by the study personnel, that includes physicians, clinical decision support investigators and/or tumor board members.

Drugs in clinical trials and/or off-label drugs will be added to the drug list as soon as they become available; and they can be assigned to patients.
## Impact2 PA12-1161 Current Status (I)

### Patients (as of 4/9/15)

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>131</td>
<td>Screened</td>
</tr>
<tr>
<td>37</td>
<td>Consented</td>
</tr>
<tr>
<td>27</td>
<td>Completed Molecular Testing</td>
</tr>
<tr>
<td>1</td>
<td>Pending Molecular Testing</td>
</tr>
<tr>
<td>4</td>
<td>Screen Fails/Withdrew Consent</td>
</tr>
<tr>
<td>3</td>
<td>Inadequate Cells</td>
</tr>
<tr>
<td>2</td>
<td>Pending Biopsy</td>
</tr>
<tr>
<td>Category</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>--------------------------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>No Actionable Mutations</td>
<td>12</td>
</tr>
<tr>
<td>Randomized</td>
<td>8</td>
</tr>
<tr>
<td>• Pending Initiation of Treatment</td>
<td>0</td>
</tr>
<tr>
<td>• Treated</td>
<td>7</td>
</tr>
<tr>
<td>Pts with PFS event or discontinued</td>
<td>2</td>
</tr>
<tr>
<td>• Not Treated (No financial clearance)</td>
<td>1</td>
</tr>
<tr>
<td>Pending Randomization</td>
<td>0</td>
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</tbody>
</table>
Precision Medicine

Other Clinical Trials
NSCLC: BATTLE-2

Enrollment in protocol - biopsy

Initial Adaptive Randomization
Kras mutation

Stage 1
N = 200
Prespecified markers (e.g., PI3KCA mutation; PTEN IHC)
Preclinical and clinical (BATTLE-1, 1st stage BATTLE-2) discovery markers

Statistical modeling and biomarker selection

Refined Adaptive Randomization:
“Best” Predictive Markers

Stage 2
N = 200

1. Erlotinib
2. Erlotinib + AKTi MK-2206
3. MEKi AZD6244 + AKTi MK-2206
4. Sorafenib

Primary endpoint: 8-week disease control Projected n = 400

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CCR Focus

PI: Papadimitrakopoulou, V
NCT01248247
## BATTLE-2: Stage 1. Results

<table>
<thead>
<tr>
<th>Randomized Arm</th>
<th>8-wk disease-control rate, % (Evaluable, n=167)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Eval.</td>
</tr>
<tr>
<td>Erlotinib</td>
<td>20</td>
</tr>
<tr>
<td>Erlotinib+AKT inhibitor</td>
<td>51</td>
</tr>
<tr>
<td>AKT+MEK inhibitors</td>
<td>53</td>
</tr>
<tr>
<td>Sorafenib</td>
<td>43</td>
</tr>
</tbody>
</table>

*Papadimitrakopoulou et al, ASCO 2014, Abstr. 8042*
SWOG-1400: A biomarker-driven, multi-arm phase II/III registration protocol in squamous cell lung cancer – second-line therapy

Multiple Phase II-III Arms with “rolling Opening & Closure

- PiK3CA Mut
  - Pi3Ki
  - Endpoint (Interim PFS) OS

- CCND1 ampl or CDKN2 loss + RB WT
  - CDK 4/6i
  - Endpoint (Interim PFS) OS

- FGFR ampl, Mut, Fusion
  - FGFRi+CT
  - Endpoint (Interim PFS) OS

- MET Expr
  - HGFi+E
  - Endpoint (Interim PFS) OS

TT=Targeted therapy, CT=chemotherapy (docetaxel or gemcitabine), E=erlotinib

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NCT02154490
WINATHER Trial

Global concept of WINATHER

Selection of Individualized treatments based on biological analysis of paired tumor and normal samples

- **Tumor - Metastatic lesions**
- **Matched Normal Tissue**

**Biopsies**

- **WINATHER Comprehensive Full genome investigation**
- **WINATHER predictive drug efficacy scoring**

**Arm A**
- **Oncogenic events from DNA analysis**
- **Matched molecular targeted therapies and/or inclusion in targeted drugs opened phase 1 trials**

**Arm B**
- **No oncogenic event**

**200 patients with metastatic cancers**

High toxicity management

Therapeutic choice based on predictive drug efficacy scoring
WINThER participants

**Cancer Centers**

- Gustave Roussy [France]
  Jean-Charles Soria, Coordinating PI

- MD Anderson Cancer Center [USA]
  Lia Tsimeridou, PI

- VHIO [Spain]
  Jordi Rodon, PI

- Chaim Sheba Medical Center [Israel]
  Rannan Berger, PI

- McGill Segal Cancer Center [Canada]
  Wilson Miller

- UCSD Moores Cancer Center [USA]
  Razelle Kurzrock

**Technology Partners**

- Foundation Medicine
  Gary Palmer
  NGS

- Agilent Technologies
  V Lazar
  Gene Expression, miRNA

- Ben Gurion University
  Eitan Rubin
  WINThER Data Analysis
SHIVA: A Randomized Phase II Trial Comparing Therapy Based on Tumor Molecular Profiling Versus Conventional Therapy in Patients With Refractory Cancer

Patients with refractory cancer (all tumor types) → Informed consent signed → Tumor biopsy → NGS+ Cytoscan HD +IHC → Bioinformatics → Informed consent signed → Eligible patient → Specific therapy available → Eligible patient

Non eligible patient → Molecular biology board → Cross-over

Targeted therapy based on molecular profiling

Conventional therapy at physicians' discretion

Imatinib
Everolimus
Sorafenib
Erlotinib
Dasatinib
Lapatinib
Trastuzumab
Vemurafenib
Tamoxifen
Letrozole
Abiraterone

Pl: Le Tourneau, C Institut Curie

Endpoint: PFS
Is Molecular Profiling Practice Changing?

- Potential for improving patient care
- Molecular profiling is used to guide treatment decisions
- Increasing complexity of molecular diagnosis
- Tumor heterogeneity predicts clinical outcomes
- ASCO’s CancerLinQ
- Standardized procedures and decision support systems
- Innovative clinical trial design
- Discovery of novel targeted agents
- Understanding and prevention of drug resistance

Tsimberidou, Best of ASCO Boston 2013
Conclusions

• Clinical trials in precision medicine are feasible
• Multiple trials are ongoing
• Innovative studies: correlative scientific queries
• Prospective innovative trials with adaptive design will accelerate process of drug approval (reduced cost, time, number of patients)
• Immune mechanisms, proteomics, transcriptome and epigenetic changes; Horizontal and vertical changes in tumor biology need to be considered
• Optimal big data bioinformatic analyses are necessary to implement precision medicine
Acknowledgments

IMPACT 1
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• Patients, Their Families

IMPACT 2
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• John Mendelsohn, M.D., Director, IPCT
• Funda Meric, M.D., Chair, ICT
• All collaborators and referring physicians from multiple Departments and Divisions, MD Anderson
• Sponsor: Foundation Medicine
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