Comprehensive genomic profiling in clinical practice and beyond

11 September 2017
IFEMA, Feria de Madrid, Spain
Welcome and introduction

Dr Razelle Kurzrock
Director, Center for Personalized Cancer Therapy
UCSD Medical Center, Moores Cancer Center
San Diego (United States)
Disclosures

Dr Kurzrock has research funding from Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, and Guardant, as well as consultant fees from X-Biotech and Actuate Therapeutics, speaker fees from Roche, and an ownership interest in Curematch, Inc.
Historical perspective

1940  1960  1980  2000  2020

Chemotherapy  Targeted therapy
What can patients expect from traditionally approved drugs?

• Traditionally approved drugs still offer only modest benefits in terms of survival gain and remission.

• Accumulating evidence suggests that using targeted therapy in unselected populations generally yields low response rates.
The evolution of molecular testing
Breathtaking progress in clinical management

Impact will increase as methods become more rapid and less costly, ultimately being used to generate comprehensive genomic profiles.

FISH: fluorescence in situ hybridisation; IHC: immunohistochemistry; NGS: next-generation sequencing; PCR: polymerase chain reaction; WES: whole exome sequencing; WGS: whole genome sequencing.

**The evolution of molecular testing**

*Breathtaking progress unparalleled in human history*

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</thead>
<tbody>
<tr>
<td>Time taken (start to finish)</td>
<td>13 years</td>
<td>4 years</td>
<td>4.5 months</td>
<td>~1 days</td>
</tr>
<tr>
<td>Number of scientists listed as authors</td>
<td>&gt; 2,800</td>
<td>31</td>
<td>27</td>
<td></td>
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<tr>
<td>Cost of sequencing (start to finish)</td>
<td>$ 2.7 billion</td>
<td>$ 100 million</td>
<td>&lt; $ 1.5 million</td>
<td>~ $ 1000</td>
</tr>
<tr>
<td>Coverage</td>
<td>8 - 10 x</td>
<td>7.5 x</td>
<td>7.4 x</td>
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<tr>
<td>Number of institutes involved</td>
<td>16</td>
<td>5</td>
<td>2</td>
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<td>Number of countries involved</td>
<td>6</td>
<td>3</td>
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### Agenda – Part I

*Panel discussions: Comprehensive genomic profiling in clinical practice – from NGS to tumor board and clinical decision*

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter/Moderator</th>
</tr>
</thead>
<tbody>
<tr>
<td>18:35–18:45</td>
<td>Comprehensive genomic profiling in clinical practice – creating opportunities for cancer patients</td>
<td>Giuseppe Curigliano</td>
</tr>
<tr>
<td>18:45–18:55</td>
<td>Tumor location or pathway-driven clinical decisions?</td>
<td>Federico Rojo</td>
</tr>
<tr>
<td>18:55–19:05</td>
<td>ProfiLER: how this study changes the way decisions will be taken</td>
<td>Jean-Yves Blay</td>
</tr>
<tr>
<td>19:05–19:15</td>
<td>Comprehensive genomic profiling: from patients with high unmet need to initial diagnostic</td>
<td>Rohit Lal</td>
</tr>
<tr>
<td>19:15–19:35</td>
<td>Examples of tumor board cases where comprehensive genomic profiling can have a pivotal role</td>
<td>All</td>
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</tbody>
</table>
**Agenda – Part II**

*Presentation: The future of personalised precision therapy, getting the right drug to the right patient at the right time*

<table>
<thead>
<tr>
<th>Time</th>
<th>Topic</th>
<th>Presenter/Moderator</th>
</tr>
</thead>
</table>
| 19:35–19:55| **The future of personalised precision therapy: getting the right drug to the right patient at the right time**  
*Dr Razelle Kurzrock*  
*UCSD Medical Center, Moores Cancer Center*  
*San Diego (United States)* | Razelle Kurzrock                                                          |
| 19:55–20:00| Conclusion                                                             | Razelle Kurzrock             |
Housekeeping notes

This meeting is being video recorded

Please remember to fill out the meeting evaluation form before leaving.
Comprehensive genomic profiling in clinical practice – creating opportunities for cancer patients

Prof. Giuseppe Curigliano
Head of Division of Early Drug Development
European Institute of Oncology (IEO), Milan, Italy
Disclosures

• Speaker bureau Roche, Pfizer and Samsung
Why comprehensive genomic profiling (CGP)?

- CGP is a molecular diagnostic approach able to detect multiple classes of genomic alterations in a broad range of known cancer-related genes and match them to therapeutic options using a clinically validated platform.

- Studies show that ~90% of patients have potentially actionable alterations which could be targeted by at least one drug in clinical trials.

- Interrogating patients’ tumors with CGP may provide therapeutic options for patients potentially resulting in improved outcomes.

Tumor heterogeneity: a significant challenge

• There is extensive genetic heterogeneity between and within tumors

• This is a significant challenge for personalised medicine

Access to testing is country specific

- Some countries have started initiatives to facilitate access

<table>
<thead>
<tr>
<th>Genomics England 100k Genomes</th>
<th>France Genomics 2025</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives:</strong></td>
<td><strong>Objectives:</strong></td>
</tr>
<tr>
<td>1. Ethical and transparent</td>
<td>1. Position France as one of the leading countries in personalised medicine</td>
</tr>
<tr>
<td>programme</td>
<td></td>
</tr>
<tr>
<td>2. Provide benefits of genomic</td>
<td>2. Integrate genomic medicine in clinical care</td>
</tr>
<tr>
<td>medicine to patients</td>
<td></td>
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<tr>
<td>3. Enable new scientific</td>
<td>3. Foster scientific and technological innovation</td>
</tr>
<tr>
<td>discovery and medical insights</td>
<td></td>
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<tr>
<td>4. Kick start the development</td>
<td></td>
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<tr>
<td>of a UK genomics industry</td>
<td></td>
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</tbody>
</table>

- In countries where reimbursement is not available testing is paid by patients

Access to therapy: only ~20% of known driver genes have an associated therapy

Comprehensive genomic profiling in clinical practice – creating opportunities for cancer patients

Panel discussion
Comprehensive genomic profiling can provide more therapeutic options and possibly an improved outcome

What should now drive clinical decision?

Tumor location or pathway-driven clinical decisions?

Dr. Federico Rojo
Director of Molecular Pathology and Manager of the Biobank
Fundación Jiménez Díaz, Madrid, Spain
Tumor location or pathway-driven clinical decisions?

Dr Federico Rojo
Director of Molecular Pathology and Manager of the Biobank
Fundación Jiménez Díaz, Madrid, Spain
Disclosures

• Nothing to declare
The classical approach to cancer is evolving

**2000: Breast cancer subtypes**
- Luminal A
- Luminal B
- HER2
- Basafold
- Normal

Clinical decisions based on affected tissue, histology and disease stage

**2017: Genomic drivers**
- PI3K/AKT/mTOR
- Growth Factor Receptors
  - ERBB2, EGFR, FGFR1
- Cell Cycle Regulators
  - CCND1, CDK4, RB1
- DNA Repair
  - BRCA1/2
- ER signalling

Clinical decisions based on the results of comprehensive genomic profiling

The role and impact of molecular alterations varies between tumor types

Same molecular alteration in different tumor types

Different impacts in different tumor types

- BRAF mutations are found in patients with metastatic melanoma and metastatic colorectal cancer\(^1,2\)
- In patients with BRAF-mutated metastatic melanoma, BRAF inhibitor therapy has demonstrated efficacy\(^1\)
- However, in patients with BRAF-mutated metastatic colorectal cancer, BRAF inhibitor therapy has limited efficacy\(^2,3\)
- For patients with colorectal cancer the biology of BRAF activation is more heterogeneous than in patients with melanoma\(^3\)

Pembrolizumab ▼, a drug based on tumor biomarkers, recently received FDA approval

- Traditionally in oncology approvals were based on a tumor type or a biomarker within a tumor type
- For the first time, the FDA has ‘approved a drug based on a tumor’s biomarker without regard to the tumor’s original location’
- Pembrolizumab ▼ is indicated for the treatment of patients with unresectable or metastatic solid tumors possessing a microsatellite instability-high (MSI-H) biomarker
- This represents a seismic shift in the global view of cancer

FDA news release retrieved from: https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm560167.htm [Accessed September 2017]. Image adapted from presentation by Steven Lemery at 2017 ASCO Annual Meeting. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office. Merck Sharp & Dohme Limited: pembrolizumab.
Tumor mutational burden predicts CIT response: is this the next tissue-agnostic biomarker?

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>No Patients</th>
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<tbody>
<tr>
<td>Pan Cancer</td>
<td>1804</td>
</tr>
<tr>
<td>Bladder</td>
<td>127</td>
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<tr>
<td>Breast</td>
<td>48</td>
</tr>
<tr>
<td>Colorectal</td>
<td>63</td>
</tr>
<tr>
<td>Esophagogastric</td>
<td>63</td>
</tr>
<tr>
<td>Glioma</td>
<td>117</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>76</td>
</tr>
<tr>
<td>Melanoma</td>
<td>323</td>
</tr>
<tr>
<td>NSCLC</td>
<td>472</td>
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<tr>
<td>Ovarian</td>
<td>32</td>
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<tr>
<td>Renal Cell</td>
<td>155</td>
</tr>
</tbody>
</table>

Improved survival for greater mutations

CIT, cancer immunotherapy; HR, hazard ratio; NSCLC, non-small cell lung cancer.
IMPACT Platform, MSKCC.
Tumor location or pathway-driven clinical decisions?

Panel discussion
More biomarkers are needed to guide tissue-independent options

How can we design innovative studies for that purpose?

Tumor location or pathway-driven clinical decisions?
Dr. Federico Rojo
Director of Molecular Pathology and Manager of the Biobank
Fundación Jiménez Díaz, Madrid, Spain

ProfiLER: how this study changes the way decisions are taken
Prof. Jean-Yves Blay
General Director
Centre Léon Bérard, Université Claude Bernard Lyon 1, LYRIC, Académie de Médecine
ProfiLER: how this study changes the way decisions are taken

Prof. Jean-Yves Blay
General Director
Centre Léon Bérard, Université Claude Bernard Lyon I, LYRIC, Académie de Médecine
Disclosures

- Research support and honoraria from Eisai, Eli Lilly, GSK, Ignyta, Novartis, Pharmamar and Roche
ProfiLER study uses various profiling platforms

NGS (Next Generation Sequencing)
- A 89-gene panel
  - Hot-spot mutation regions for 8 genes (AKT1, BRAF, EGFR, c-MET, HRAS, NRAS, BRAF, PIK3CA)
  - Entire coding sequences for the remaining 81 genes
- Coverage: 90%
- Average sequencing depth: 200X
- Variant calling
- GATK-based bioinformatics pipeline
- NextGene software
- Biological interpretation of variants
  - Hot-spot mutations in oncogenes
  - Actionable mutations if:
    - Records in databases (e.g. COSMIC)
    - Localization in functional domains
    - In silico prediction (SIFT, PolyPhen-2)

aCGH (Comparative Genomic Hybridization)
- Analysis of somatic copy-number variation (CNV) on Agilent platform
- Detection of CNV only if:
  - No detection of balanced alterations (inversions, balanced translocations, ...)
  - No detection of copy neutral loss of heterozygosity (CN-LOH)
- Fail to detect haploid or polyploid genomes

Trédan, O., et al. ASCO 2017 #LBA100.
Only 7% of patients received treatment based on profiling

- Enrolled: N = 2676
- Tumor genomic profiles: N = 1944
- At least one actionable alterations: N = 1004 (52%)
- At least one MTA recommended: N = 676 (35%)
- Patients treated with recommended MTA: N = 143 (7%)
- Premature withdrawals: N = 416 (16%)
  - Tumor sample not exploitable, n = 339
  - Less than 10% tumor cells, n = 19
  - DNA extraction issues, n = 19
  - aCGH or NGS failures, n = 13
  - Other reasons, n = 31
- No recommendation: N = 328 (33%)
  - MTA not available, n = 135
  - MTA previously administered, n = 30
  - Early death, n = 65
  - Others, n = 98

Overall survival in patients with targeted therapy

Median [IC95%]: 3.3 years [2.7 ; 4.3]
5-year survival rate [IC95%]: 34.8% [26.2-43.6]
ProfiLER 02 study compares FoundationOne® against an academic gene panel

Overall design and objectives

ICF Signature
Collection of tumor sample
Randomisation

MOLECULAR TUMOR BOARD
INITIATION OF MTT

At time of relapse

PANEL Foundation Medicine
PANEL INCa

TRANSLATIONAL PROGRAM
COLLECTION OF CLINICAL DATA
HEALTH ECONOMIC EVALUATION

(same molecular profiling using ctDNA)
ORR4m, DoR, DCR4m, PFS and OS, safety
Tumor growth kinetics and QoL
Cost of NGS-driven therapy
Cost-effectiveness analysis
Utility of a molecular tumor board
Leveraging interdisciplinary expertise

- Expansion of physicians’ comfort zones arguably presents the most formidable challenge to implementing precision medicine\(^1\)

- A molecular tumor board combines specialists from multiple disciplines\(^2\)

- The systematic, multidisciplinary overview of a molecular tumor board may enhance successful use of the rapidly evolving spectrum of targeted agents\(^2\)

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ProfiLER: how this study changes the way decisions are taken

Panel discussion
Molecular diagnostic trials show the need for a paradigm change

How can we match patients to therapies and ensure we identify them early enough?

Comprehensive genomic profiling: from patients with high unmet need to initial diagnostic

Dr Rohit Loi
Consultant medical oncologist
Guy’s and St Thomas’ NHS Foundation Trust, London, UK
Comprehensive genomic profiling: from patients with high unmet need to initial diagnostic

Dr Rohit Lal
Consultant medical oncologist
Guy’s and St Thomas’ NHS Foundation Trust, London, UK
Dr Rohit Lal - Disclosures

Conference registration, travel and accommodation
• Roche – FMI
• MSD
• Boeringher-Ingelheim
• Eli-Lilly

Advisory honoraria
• Astra Zeneca
• Roche
• Pfizer
Comprehensive genomic profiling is currently used conservatively

- **Which patients** should receive profiling?
- Current practice is for profiling only to be used in patients with **high unmet need**
- Potential **scenarios within advanced NSCLC**
  - Only EGFR/ALK-negative non-smokers at diagnosis?
  - Only EGFR/ALK-negative, stage IV at diagnosis?
  - All stage IV patients at diagnosis?
Genomic EGFR testing informs adjuvant use of TKI

Disease-free survival (%)

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>No. at risk: Gefitinib</th>
<th>Events</th>
<th>Median, months (95% CI)</th>
<th>No. at risk: Vinorelbin plus cisplatin</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>111</td>
<td>65</td>
<td>28.7 (24.9, 32.5)</td>
<td>111</td>
<td>59</td>
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<tr>
<td>12</td>
<td>88</td>
<td></td>
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<td>54</td>
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<tr>
<td>60</td>
<td>0</td>
<td></td>
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</table>

HR for recurrence = 0.60
95% CI 0.42, 0.87; p = 0.005

3-year DFS rate: 34% vs 27%

Δ 10.7 m

Adjuvant gefitinib is correlated with extended disease free survival in NSCLC patients with EGFR-activating mutations.
Many patients with actionable mutations do not receive matched therapy

<table>
<thead>
<tr>
<th>Series</th>
<th>Actionable mutation</th>
<th>Received matched drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSKCC-IMPACT (Nat Med 2017); n = 10,336</td>
<td>38%</td>
<td>11%</td>
</tr>
<tr>
<td>MDACC (Cancer Res 2016); n = 500</td>
<td>95%</td>
<td>24%</td>
</tr>
<tr>
<td>MDACC (JCO 2015); n = 2,000</td>
<td>39%</td>
<td>4%</td>
</tr>
<tr>
<td>MDACC (CCR 2012); n = 1,144</td>
<td>40%</td>
<td>15%</td>
</tr>
<tr>
<td>Princess Margaret-IMPACT-COMPACT (Genome med 2016); n = 1,640</td>
<td>57%</td>
<td>5%</td>
</tr>
<tr>
<td>Johns Hopkins (Sci Transl Med 2015); n = 753</td>
<td>77%</td>
<td>NR</td>
</tr>
<tr>
<td>PREDICT-UCSD (Mol Cancer Ther 2016); n = 347</td>
<td>NR</td>
<td>25%</td>
</tr>
<tr>
<td>Cleveland Clinic (JNCI 2016); n = 250</td>
<td>49%</td>
<td>11%</td>
</tr>
<tr>
<td>Vanderbilt (Oncologist 2014); n = 103</td>
<td>83%</td>
<td>25%</td>
</tr>
<tr>
<td>Indiana University (ASCO 2017); n = 139</td>
<td>85%</td>
<td>21.6%</td>
</tr>
<tr>
<td><strong>Range (mean)</strong></td>
<td><strong>38%-95% (44%)</strong></td>
<td><strong>4%-25% (11%)</strong></td>
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NGS testing may be most beneficial early in disease management

0-1\textsuperscript{st} line: 29.2 %, \( P = 0.04 \)
2\textsuperscript{nd}+ lines: 17.2 %

**Schneider, B.P. (2017) ASCO Clinical Science Symposium. Abstract number 102.**

**Ammakanavar, N. (2017) ASCO Clinical Science Symposium. Abstract number 102.**
Genomic profiling should be considered a tool for improving outcomes from the start

• Use of comprehensive genomic profiling as an initial diagnostic could alter the disease course by:
  – improving the accuracy of diagnosis
  – helping determine prognosis
  – predicting response to certain therapies
  – enabling avoidance of chemotherapy and its associated side effects

• Genomic profiling could also be useful at disease progression to enable identification of resistance mutations
Comprehensive genomic profiling: from patients with high unmet need to initial diagnostic

Panel discussion
Examples of tumor board cases where comprehensive genomic profiling can have a pivotal role

*Panel discussion*

The information contained herein may refer to use of products for indications other than those approved and/or listed in the Summary of Product Characteristics or relating to molecules currently undergoing experimental trials. The issues addressed are not meant to suggest that these products be employed for indications other than those authorised.
Clinical case

Dr Rohit Lal
Consultant medical oncologist
Guy’s and St Thomas’ NHS Foundation Trust, London, UK
Clinical case: lung adenocarcinoma

Patient medical background and initial diagnostic

Medical background

- Caucasian male
- 72 years old
- Persisting cough

Initial diagnostic (November 2012)

- Lung adenocarcinoma – lepedic variant
- T2N0M0 (PET/CT)
Clinical case: lung adenocarcinoma

Initial medical decision

Initial surgery
13 November 2012

- Left lower lobectomy and left upper lobe segmentectomy with mediastinal lymph node clearance
- Stage 3a pT2N2M0 - complete resection

Therapy selected
November 2012

carboplatin vinorelbine
3 times weekly x 4
Clinical case: lung adenocarcinoma
Follow up and new medical decision

CT scan
August 2014

Single gene molecular profiling

EGFR ex19 mutation

Therapy change
September 2014

afatinib ▼ 40 mg once a day
Cycle 3 dose reduction to 30mg once a day

CT, computed tomography. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local Boehringer Ingelheim International GmbH office.
Clinical case: lung adenocarcinoma

Patient follow-up

CT scan
June 2015

Maintained partial response

Therapy change
January 2016

G3 paronychia requiring dose interruption and reduction

CT scan
April 2016

Small volume relapse in lung and brain

Surgical biopsy for CGP

CT, computed tomography; CGP, comprehensive genomic profiling.
Panel discussion

Based on the patient status, what would you advise?
Clinical case: lung adenocarcinoma

Local molecular profiling platform report (24 genes) – May 2016

MOLECULAR ANALYSIS

NGS SOMATIC MUTATION ANALYSIS REPORT (UCL Advanced Diagnostics) MA16-737:

DETECTED VARIANTS (Percentage of Total DNA >2.5%)
EGFR p.(Glu746_AlA750del), c.2236_2250del, COSM6225 (16.24%)
EGFR p.(Thr790Met), c.2369C>T, COSM6240 (7.35%)
PIK3CA p.(His1047Arg), c.3140A>G, COSM775 (6.33%)
TP53 p.(Pro72Arg), c.215C>G, COSM250061 (57.01%)

SUMMARY COMMENTS
EGFR p.(Glu746_AlA750del), this deletion in Exon 19 has been associated with increased resistance to EGFR TKIs in non-small cell lung cancer.
EGFR p.Thr790Met, this mutation which is rarely (<5%) found in untreated EGFR-mutated tumours, has been associated with decreased sensitivity to 1st and 2nd generation TKIs in non-small cell lung cancer.

No other variants with currently established therapeutic implications for NICE approved therapies were detected in this specimen. Specifically, these include BRF (Codon 600), EGFR (Codons 719, 858, 861, exon 19 insertions or exons 20 insertions), KRAS (Codons 12,13, 59, 61, 117 & 146), and NRAS (Codons 12, 13, 59 & 61).

ALK IMMUNOHISTOCHEMISTRY (p16-6610)
Negative.

FISH TESTING FOR ROS1 CHROMOSOMAL TRANSLOCATION (P16-6610)
Evidence of negative signal profile.
Mean ROS1 gene/cell: 1.66
Panel discussion

After seeing the molecular profiling report results, would you change your treatment strategy?
Clinical case: lung adenocarcinoma

Medical decision

Therapy selected
May 2016

osimertinib ▼ daily oral
21 days

CT scan
January 2017

Chest abdomen pelvis (CAP) scan:
partial response in lungs

Head scan:
complete response

CT Scan
April 2017

Maintained complete response

CT, computed tomography. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your local AstraZeneca AB office.
Clinical case: conclusions

- Multiple actionable mutations
- Actionable resistance mutations
- Treatment options available for the patient
The future of personalised precision therapy: getting the right drug to the right patient at the right time

Dr Razelle Kurzrock
Director, Center for Personalized Cancer Therapy
UCSD Medical Center, Moores Cancer Center
San Diego (United States)
What we have learnt

• Tumor heterogeneity and access to therapy present significant challenges for personalised medicine

• While approval of pembrolizumab is a major advance, more biomarkers are needed

• Use of a molecular tumor board, as instituted in the ProfiLER study, may enhance successful drug acquisition

• Comprehensive genomic profiling should not be considered as a “last resort”

Comprehensive genomic profiling to improve diagnosis and therapy selection in cancer patients: getting the right drug to the right patient at the right time
Mobile multifaceted targeting against cancer

• Advanced molecular profiling for every patient, repeated frequently

• Match patients with the right drug(s) – personalized/precision therapy

• Cancer can be complex; use customized combination treatments

• Treat earlier in the course of the disease – the leukemia (CML) model

• Emancipate the immune system
What happens in a precision medicine clinic

Classic
- IHC
- FISH
- PCR

Comprehensive molecular profiling
- Next-Generation DNA sequencing
- Protein analysis
- Immune signature analysis
- Liquid biopsy (cancer DNA detection from blood)

“MATCH” the therapy based on the profiling
Personalized/Precision Medicine approach

Adapted from Toward precision medicine, NAS 2013.
Meta analysis of ~85,000 patients in Phase I, II and III trials

Targeted therapy in of itself is not generally effective – a biomarker is needed

<table>
<thead>
<tr>
<th>ARMS type</th>
<th>Pooled Analysis</th>
<th>Meta-analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RR (%)</td>
<td>PFS (Mos)</td>
</tr>
<tr>
<td>Non-personalized targeted</td>
<td>4</td>
<td>2.6</td>
</tr>
<tr>
<td>Cytotoxic</td>
<td>12</td>
<td>3.3</td>
</tr>
<tr>
<td>Personalized targeted</td>
<td>30</td>
<td>6.9</td>
</tr>
</tbody>
</table>

Worst outcome

Best outcome

Master protocol
Profile-Related Evidence Determining Individualized Cancer Therapy

PREDICT

- Histology-independent targeted approach
- Multiple molecular aberrations assessed
- Patients matched with targeted agents
Matching patients with targeted drugs increases response rates

Matched therapy
N = 175
Complete/Partial Response = 27%

CR: 4 (2%)
PR: 43 (25%)
SD > 6m: 40 (23%)

Therapy without matching
N = 116
Complete/Partial Response = 5%

CR: 0 (0%)
PR: 6 (5%)
SD > 6m: 12 (10%)

P < .0001

Redesigning cancer trials: Stage 1

Smaller Trials, Bigger Chance for Success

**OLD MODEL:** Large numbers of patients, not selected by molecular characteristics; lower chance of demonstrating effectiveness, since many participants do not have the molecular defects being targeted

**NEW MODEL:** Small patient populations, all with the relevant mutations or genetic defects; greater chance of desired results, since all participants have the potential to respond

Fundamental premise

*Every metastatic tumor is complex and unique*
Pt number | Molecular results (Foundation Medicine)
---|---
1 | PIK3CA amplification, SOX2 amplification, TP53 G302fs*42, FLT3 L260*
2 | AKT1 (E17K)
4 | EGFR amplification, CCND1 amplification, CDKN2A/B loss, FGFR1 amplification, MYC amplification, TP53 P151A
42 | ERBB2 amplification, PIK3CA H1047L, AURKA amplification, TP53 R342P, CREBBP P858S, ZNF217 amplification
25 | ERBB2 amplification, MYC amplification, CDK6 amplification, TP53 R213*
7 | ESR1 Y537S
13 | GATA3 *445fs*2+
16 | RET C634R, GATA3 P436fs*11+
18 | AKT3 amplification, MYC amplification, MYCL1 amplification, TP53 R248Q
54 | NF1 R1276Q

Malignant snowflakes

Drug-centric trial (traditional)

**Strategy:** Find common feature between patients (e.g. type of cancer or type of molecular aberration) and place all on same drugs
Patient-centric trial (N-of-one)

**Strategy**: Molecular matching for each patient with customized therapy combination

- **Patient 1**: Aberrant A, B, C
  - Drug A
  - Drug B
  - Drug C

- **Patient 2**: Aberrant A, E, F
  - Drug A
  - Drug E
  - Drug F
**Patient-centric trial (N-of-one)**

**Strategic**: Molecular matching for each patient with customized therapy combination

- **Patient 1**: Arthritis, Heart, Diabetes
  - Tofacitinib ▼
  - Prozac
  - Digoxin
  - Metformin ▼

- **Patient 2**: Arthritis, Depression, Infection
  - Tofacitinib ▼
  - Penicillin

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective Roche local office. Pfizer Limited: tofacitinib; Boehringer Ingelheim International GmbH or Takeda Pharma A/S or Janssen-Cilag International NV or Bristol-Myers Squibb / AstraZeneca EEIG: Metformin
Are combinations of drugs safe?

Patient R with breast cancer HER2+

- Ado-trastuzumab emtansine (TDM1) ▼ → remission

- At relapse found to have a PIK3CA mutation

- Everolimus to be added → but “no phase I study demonstrating the safety of TDM1 and everolimus combination”


Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective Roche local office.
Where is the safety data?

- TDM1 (ado-trastuzumab emtansine) ▼
- Alprazolam
- Arformoterol tartrate
- ASA
- CoQ10
- Folate / Vit B6 / Vit B12
- Levothyroxine
- Beclomethasone dipropionate
- Tiotropium bromide ▼
- Bupropion
- Benzonatate
- Saliva substitutes topical
- Dextromethorphan and guaifenesin
- Ipratropium nasal
- Levalbuterol
- Spironolactone
- Fondaparinux

Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective local office. Roche: TDM1; Orexigen Therapeutics Ireland Limited: bupropion; Boehringer Ingelheim International GmbH: Tiotropium Bromide Monohydrate
Lessons from the chronic myelogenous leukemia (CML) story

A fatal disease transformed

- **93%**
- **84%**

<table>
<thead>
<tr>
<th>Year</th>
<th>Total</th>
<th>Dead</th>
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</thead>
<tbody>
<tr>
<td>1975-1981</td>
<td>302</td>
<td>15</td>
</tr>
<tr>
<td>(censored for non-CML death)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1975-1981</td>
<td>302</td>
<td>31</td>
</tr>
<tr>
<td>Imatinib</td>
<td>132</td>
<td>129</td>
</tr>
<tr>
<td>1975-1981</td>
<td>132</td>
<td>129</td>
</tr>
</tbody>
</table>
Treatment of medulloblastoma with hedgehog pathway inhibitor GDC-0449

Figure 1. Tumor Response on Positron-Emission Tomographic (PET) Scanning.
Whole-body projections from $^{18}$F-fluorodeoxyglucose (FDG)-PET scans are shown. Panel A shows the pretreatment scan; Panel B, the repeat scan after 2 months of therapy with the hedgehog pathway inhibitor GDC-0449; and Panel C, the repeat scan after 3 months of therapy.

Response rate of chronic myelogenous leukemia rises rapidly in newly diagnosed disease

Key factors leading to the revolution in outcome of chronic myelogenous disease

- Key factors:
  - Known driver target (Bcr-Abl)
  - Targeted agent (imatinib▼)
  - Treat newly-diagnosed patients

Key factors leading to the revolution in outcome of chronic myelogenous disease

Response rates to immunotherapy and tumor mutational burden (TMB) across cancers

- 4% for low TMB (0-5 mut/MB)
- 26% for intermediate TMB (6-19 mut/MB)
- 45% for high TMB (20-49 mut/MB)
- 67% for very high TMB (≥50 mut/MB)

Some patients with advanced, refractory cancers attain long-term remissions (¿ cure)

Mut/MB, mutations per megabase.
The pillars of precision medicine

Genomics  Immunotherapy

The future is here

T-cell killing cancer cell
Thank you for your time and interest

rkurzrock@ucsd.edu
teoam2011@gmail.com
The future of personalised precision therapy: getting the right drug to the right patient at the right time

Q&A
Conclusion

Dr Razelle Kurzrock
Director, Center for Personalized Cancer Therapy
UCSD Medical Center, Moores Cancer Center
San Diego (United States)
The future of personalised therapy

- Targeted therapy in of itself is not effective
- Insulin is a great drug but not if given to patients with pneumonia
- Pneumonia would be viewed as a difficult disease to treat if insulin and heart medications were given to the patients

It is about matching patients with the right therapy
Clinical trial design is evolving

**Basket**
One gene: Different histologies

**Umbrella**
One histology: Different genes

**Octopus**
One study: Multiple arms
MyPathway study: Multi-basket study

Total enrollment is 354, at 45 sites, as of August 15, 2017
3 months ahead of predicted enrollment

Overall target accrual: 500
Primary endpoint: ORR
Secondary endpoints: PFS, OS, CBR

CBR, clinical benefit rate; ORR, objective response rate; OS, overall survival; PFS, progression-free survival. NCT02091141: An open label phase IIa study evaluating trastuzumab/pertuzumab, erlotinib, vemurafenib/cobimetinib, vismodegib, alectinib and atezolizumab in patients who have advanced solid tumors with mutations or gene expression abnormalities predictive of response to one of these agents. Therapies marked with ▼ are subject to additional monitoring. Reporting suspected adverse reactions after authorisation of the medicinal product is important. Adverse events should be reported to your respective Roche local office.
What happens in a precision medicine clinic

Classic
- IHC
- FISH
- PCR

Comprehensive molecular profiling
- Next-Generation DNA sequencing
- Protein analysis
- Immune signature analysis
- Liquid biopsy (cancer DNA detection from blood)

“MATCH” the therapy based on the profiling
Personalized/Precision Medicine approach

Adapted from Toward precision medicine, NAS 2013.
The precision medicine era

- Advanced molecular profiling for every patient, repeated frequently
- Match patients with the right drug(s) – personalized/precision therapy
- Cancer can be complex; use customized combination treatments
- Treat earlier in the course of the disease – the leukemia (CML) model
- Emancipate the immune system
Thank you for your participation
Please remember to fill out the meeting evaluation form before leaving
Doing now what patients need next