The Era of Precision Cancer Medicine: A worldwide effort and challenge
Introduction to WIN Consortium

June 29, 2015

Dr. John Mendelsohn
Chairman of WIN Consortium
In institutions screening large numbers of cancers for genetic aberrations, only about 10% of patients end up enrolled in a clinical trial with a targeted therapy.

Research is achieving progress with new targeted molecules, and in particular with modulators of immune checkpoints.

Major new trials are being launched that will bring more targeted therapies to more patients, eg., NCI MATCH, LUNG MAP, ALCHEMIST and many others.
Limitations

• Targeted therapies can produce high response rates, but typically limited to small subsets of patients

• Responders often develop resistance and succumb to their disease

→ Overall, the impact on survival remains limited for most types of cancer

Next Challenges

• Explanations of sensitivity and resistance

• Panels of “omic” biomarkers predicting therapeutic efficacy

• Algorithms to predict optimal therapeutic combinations

• Trials of safe and potentially effective combination therapies
Our common aspirational goals

• Improve patient access to precision medicine

• A dramatic impact on survival

No institution can achieve this alone
WIN Consortium

*We can accomplish more together than each organization can achieve working alone*

A world wide network assembling all cancer stakeholders to develop cutting edge concepts in precision cancer medicine to *impact survival for cancer patients*

www.winconsortium.org
WIN members include

- 27 Academic Cancer Centers in 17 countries on 4 continents
- 9 pharmaceutical and technology companies
- 5 cancer charities, not-for-profits and health payors

Main Assets

- Outstanding expertise in clinical research
- Diverse patient populations
- Participation of representatives of all stakeholders
# Executive Committee
## 2014-2015

<table>
<thead>
<tr>
<th>Name</th>
<th>Position</th>
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<tbody>
<tr>
<td>John Mendelsohn</td>
<td>Chairman</td>
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<tr>
<td>Alexander Eggermont</td>
<td>Vice Chair</td>
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<tr>
<td>Richard L. Schilsky</td>
<td>Chair, Scientific Advisory Board</td>
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<tr>
<td>Razelle Kurzrock</td>
<td>Head of Clinical Trials Committee</td>
</tr>
<tr>
<td>Vladimir Lazar</td>
<td>Chief Operating Officer</td>
</tr>
<tr>
<td>Catherine Bresson</td>
<td>Director, Operational Team</td>
</tr>
<tr>
<td>Waun Ki Hong</td>
<td>Special Advisor</td>
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Scientific Advisory Board

Richard L. Schilsky, Chair
J. Jack Lee, MD Anderson Cancer Center
Gidi Rechavi, Sheba medical Center
Soonmyung Paik, Yonsei University College of Medicine
Stephen Laderman, Agilent Technologies
Jin Li, Fundan University Cancer Hospital Shanghai
Stanley Hamilton, MD Anderson Cancer Center
Sabine Tejpar, EORTC
Yosef Yarden, Weizmann Institute
Yudi Pawitan, Karolinska Institutet
Leroy Hood, Institute of Systems Biology
Phillip Febbo, Genomic health
Gary Rosner, Sidney Kimmel CCC Johns Hopkins
Yves Lussier, University of Arizona
John Quackenbush, Dana Farber
Manfred Schmitt, Universitae Munchen
Lillian Siu, Princess Margaret Hospital
Pasi Jane, Dana Farber
What WIN does

• WIN shares information to promote investigation and use of personalized, targeted cancer therapy through the annual WIN symposia and publications.

• WIN launches breakthrough trials with the aim to enable moving from a target or pathway driven therapeutic approach to a systems biology approach, with combinations of biomarkers and combinations of therapies.
Symposium
WIN2015

Sessions will focus on some of the major advances:

- Immunomodulation
- Multi-modality and multi-drug cancer therapy
- New avenues: Big trials and big data
- Regulatory and funding challenges in the era of personalized cancer medicine
- Etc.

Speakers represent a variety of organizations, eg.,

- James Allison, MDACC
- James Doroshow, NCI
- Francesco Pignatti, EMA
- Tatiana Prowell, FDA
- Peter Yu, Past-President ASCO
To orient patients to a personalized treatment we:

Evaluate both

- **Structural DNA** – actionable genetic aberrations will at best represent 40% of cancers

  and

- **RNA expression levels** - WINTHER explores altered gene expression as a solution for those with no actionable DNA structural changes

- We introduce the investigation of the **normal matched tissue** from the patient, as the optimal control
HORIZON 2020
The EU Framework Programme for Research and Innovation

Matching drug to patient
Published by newsroom editor on Thursday, 07/05/2015

Lung cancer is the leading killer of all cancers worldwide. The outcome depends heavily on when the disease is diagnosed. But therapeutic strategies are also key, and those currently available are only making modest inroads into mortality rates. The EU-funded project WINther set out to improve methods for predicting the efficacy of drugs in cancer patients in a ground-breaking new approach to targeted therapies.

Today, cancer-targeted therapies are primarily aimed at tackling detected oncogenic mutations or other DNA aberrations. However, only 40% of patients benefit from this approach, because targetable DNA anomaly cannot be detected in all cases.

Within the WINther project, an international team of researchers coordinated by Jean-Charles Soria of the Gustave Roussy Institut in France complemented the traditional DNA-based approach with RNA-based investigation, effectively enabling personalised therapy for those patients with any kind of advanced solid malignant tumour that does not display any targetable DNA anomaly.

To this effect, WINther introduced – and this was a first in a clinical trial – the concept of dual biopsies from the tumour and the normal tissue with which it had been matched to see how messenger RNA (mRNA) is expressed differently in the two. The assumption made was that drugs targeting those tumour genes which showed the greatest difference compared with the normal tissue would be most effective.

Filtering out genetic background noise

“When a tumour biopsy is investigated by measuring levels of mRNA, it is not possible to distinguish between the ‘genetic background noise’ and the useful information related to tumour-intrinsic abnormalities. Thanks to the dual biopsy, WINther was able to filter out this background noise,” says Gustave Roussy’s Vladimir Lazar, scientific coordinator of WINther and a founder of the WIN Consortium, in which WINther is embedded.

“The WIN Consortium, a joint project of the Gustave Roussy Institute and the MD Anderson Cancer Center in the USA, brings together 40 members from across the globe, aiming to achieve together what no institution can achieve alone: significantly improving patient survival rates,” Alexander Eggermont, General Director of Gustave Roussy and Vice Chair of the WIN Consortium, explains.

“We are grateful for the visionary support of EU for WINther,” adds WIN Chairman John Mendelsohn of MD Anderson Cancer Center and part of the WINther coordination team.

Although the trial is still on going, it already suggests that this mRNA-based strategy is in no way inferior to the standard DNA-based approach when it comes to performance. However, WINther – just like other monotherapeutic approaches in which only a single therapy is used – provides only modest benefit for patients overall.
WIN next generation trials

Focused on Lung cancer: the deadliest cancer

Addressing NSCLC at all stages of the disease

Biomarkers Early detection

Innovative therapy Cure

5 year survival Good quality of life

Systems Medicine (SIMS)

Marketers for early detection

Reduce relapse with dual-adjuvant therapy

Biomarker driven Tri-therapy

Stage I & II a (15%)

Surgery + Observation

80% alive at 5 years

Stage II b & III a (25%)

Surgery + Adjuvant chemo

40% alive at 5 years

30% relapse within 12 months

Stage III b & IV (60%)

Radiation + Chemo

5% alive at 5 years

Median survival 12 months

Building on WINther’s lessons
WIN trials aim to

• Bring personalized therapy to a larger number of patients *now*, by introducing novel concepts and tools to assign therapies

• Investigate the latest targeted drug discoveries with our pharmaceutical members

• Contribute to building the technologies of the future with our technology members

• Accelerate the implementation of clinical trials with targeted agents, involving the use of structural and functional omics

• Promote sharing of information

• Take precision medicine to the next level with combinations of therapies that may impact survival for a larger number of patients
<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1944</td>
<td>The genetic material is DNA.</td>
</tr>
<tr>
<td>1953</td>
<td>Structure of DNA.</td>
</tr>
<tr>
<td>1960s</td>
<td>The genetic code and machinery.</td>
</tr>
<tr>
<td>1970s</td>
<td>Manipulating and sequencing DNA.</td>
</tr>
<tr>
<td></td>
<td>Cancer is a genetic disease with Darwinian clonal evolution.</td>
</tr>
<tr>
<td>1980s</td>
<td>Oncogenes and suppressor genes. Therapies targeting products of aberrant genes.</td>
</tr>
<tr>
<td>1990s</td>
<td>Sequencing of the human genome.</td>
</tr>
<tr>
<td>2000s</td>
<td>Genomic medicine in the clinic.</td>
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</table>
Personalized Cancer Therapy – Recent Successes Involved Biomarkers

1. **Trastuzumab** for high-HER2 breast cancer. Slamon, NEJM, 2001
4. **Gefitinib** against the EGF receptor as first line therapy for advanced NSCLC. Mok, NEJM 2009
M.D. Anderson Cancer Center
Sheikh Khalifa Institute for Personalized Cancer Therapy:
Goals

1. Create the infrastructure and platforms for genetic analysis of large numbers of clinical cancer specimens.
2. Support clinical trials bringing therapies to patients that target the genetic aberrations in their cancers.
3. Provide decision support to create personalized cancer treatment plans.
4. Demonstrate the value of this approach so that it will become standard of practice and reimbursed.
5. Educate the next generation of clinical investigators.
IPCT Clearinghouse Protocol

All potentially eligible patients consented & physician notified

Archival block requested
  Biopsy only if clinically indicated or part of trial

T200
Oncologists has access to research data

CLIA validation of clinically relevant findings

CMS46
Actionable Aberration

Standard of care treatment
Or
Active umbrella trials
Or
Phase I, II, III trials

Clinical trial support
• Data capture and database development
• Clinical trial alert
• Track trial enrollment
• Response and survival
• Call-back program
### Potentially Actionable Genomic Aberrations in Patients Screened with CMS46: first 2,000 patients

<table>
<thead>
<tr>
<th>Description</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potentially actionable somatic mutations (not including TP53)</td>
<td>39%</td>
</tr>
<tr>
<td>Non-actionable somatic mutations</td>
<td>21%</td>
</tr>
<tr>
<td>Likely germline variants</td>
<td>10%</td>
</tr>
<tr>
<td>No mutations/variants</td>
<td>30%</td>
</tr>
</tbody>
</table>

Patients treated on genotype matched trials 11%
2000 patients likely to enter trials
Hot Spot Mutation CMS46 (Ion Torrent)
Potentially actionable 39%
TP53 not counted (31%) KRAS counted (11%) Oct 2014

Most targetable aberrations are rare across cancers
Frequency of Potentially Actionable Alterations by Tumor Type on CMS46 Varies by Tumor Type (Not counting p53)

<table>
<thead>
<tr>
<th>Disease</th>
<th>% ofPts with Actionable by Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pancreatic</td>
<td>78.9</td>
</tr>
<tr>
<td>Melanoma</td>
<td>77.2</td>
</tr>
<tr>
<td>Colorectal</td>
<td>66.9</td>
</tr>
<tr>
<td>Thyroid</td>
<td>53.8</td>
</tr>
<tr>
<td>Lung</td>
<td>52.8</td>
</tr>
<tr>
<td>Endometrial</td>
<td>50.0</td>
</tr>
<tr>
<td>Breast</td>
<td>33.1</td>
</tr>
<tr>
<td>Ovarian</td>
<td>22.2</td>
</tr>
<tr>
<td>Head &amp; Neck</td>
<td>21.4</td>
</tr>
<tr>
<td>Brain</td>
<td>20.9</td>
</tr>
<tr>
<td>Esophageal</td>
<td>16.0</td>
</tr>
<tr>
<td>Gastric/Stomach</td>
<td>15.8</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>8.3</td>
</tr>
<tr>
<td>Prostate</td>
<td>6.7</td>
</tr>
<tr>
<td>Sarcoma</td>
<td>6.0</td>
</tr>
<tr>
<td>Renal</td>
<td>5.0</td>
</tr>
</tbody>
</table>
Recruiting Basket Trials to MDACC

T200

BRCA1/2 mutation/deletion (49/525)

ALK mutant 30/525

TSC1/2 17/528

mTOR 13/525

AKT AMP 47/525

G. Mills
Unusual Responder Protocol

• Support for biopsies of unusual responders to targeted therapies and molecular profiling:
  1) Exceptional responders (compared with non-responders)
  2) Patients who had tumor progression after a partial or complete clinical response
  3) Patients with mixed response (partial response in one accessible tumor, with progression of another accessible lesion)
  4) Patients with unexpected rapid progression
  5) Survivors free of disease, who have a late relapse
Major Challenges for the Future

1. **More trials, including combinations of therapies**
   - Discover better and more accessible (circulating) biomarkers.
   - Plan and support trials targeting infrequent, likely-actionable aberrations.
   - Identify optimal combinations based on biomarker results, using computational and systems biology.
   - Plan and support combination trials with drugs from multiple pharmaceutical companies.
   - Plan efficient studies of toxicity, efficacy and optimal sequencing of combinations of therapies.
Examples of “next-generation clinical trials”

<table>
<thead>
<tr>
<th>Trial</th>
<th>Participants</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung-MAP single agent</td>
<td>4 NCTC groups</td>
<td>Umbrella trial for recurrent squamous lung cancer</td>
</tr>
<tr>
<td>NCI-MATCH single agent</td>
<td>4 NCTC groups</td>
<td>Parallel basket trials – all cancers, one drug in each basket</td>
</tr>
<tr>
<td>NCI-MPACT combinations</td>
<td>4 NCTC groups</td>
<td>Randomized – drugs matching or not matching target identified in the cancer</td>
</tr>
<tr>
<td>I-SPY2 combinations</td>
<td>Consortium – Fdn NIH</td>
<td>Umbrella phase II neoadjuvant trial for high risk breast cancer – 8 subsets, adaptively randomized, 6 arms at a time. Chemo plus an experimental drug</td>
</tr>
</tbody>
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D. Berry
2. **Information management and sharing**

- Massive amounts of clinical and research data to collect, analyze and store.
- Lack of standardization and interoperability of laboratory and clinical data.
- Data often balkanized in silos. Academicians unwilling to share data early, due to “career development.” Companies unwilling to share data early due to product development.
- Need to gather data into a vast “knowledge network” to create a research computational platform.
- Need decision support tools for oncologists and their patients.
Personalized cancer therapy is a treatment strategy centered on the ability to predict which patients are more likely to respond to specific cancer therapies. This approach is founded upon the idea that tumor biomarkers are associated with patient prognosis and tumor response to therapy. In addition, patient genetic factors can be associated with drug metabolism, drug response and drug toxicity. Personalized tumor molecular profiles, tumor disease site and other patient characteristics are then potentially used for determining optimum individualized therapy options.

Tumor biomarkers can be DNA, RNA, protein and metabolomic profiles that predict therapy response. However, the most recent approach is the sequencing of tumor DNA, which can reveal genomic alterations that have implications for cancer treatment. This Personalized Cancer Therapy website was specifically developed as a tool for physicians and patients to assess potential therapy options based on specific tumor biomarkers.

Funda Meric-Bernstam