WIN THER Study

Jean-Charles Soria, Razelle Kurzrock, Josep Tabernero, Apostolia Tsimberidou, Jordi Rodon, Raanan Berger, Amir Onn, Gerald Batist, Eitan Rubin, Yohann Loriot, Catherine Bresson, Vladimir Lazar
WINTHER:

A study to select rational therapeutics based on the analysis of tumor and matched normal tissue biopsies in subjects with advanced malignancies
Position of the problem and clinical challenges to be addressed
How can we improve cancer care for 60 to 70% of pts?

Match with targeted therapies

Relevant DNA structural changes 30 to 40% of pts

Tumor Biopsy

Standard Pathology

Standard Protocols

DNA investigations

Personalized Medicine

Today
State of the Art
State of the Art

Patient with metastatic cancer

TUMOR BIOPSY

Histology Control

MOLECULAR PROFILING

Mutational aberrations

CGH

Deep sequencing

% of cancer cells

TREATMENT BASED ON DNA BIOLOGICAL INVESTIGATIONS OF THE TUMOR
WINTHER concept
Patient with metastatic cancer

TUMOR BIOPSY & MATCHED NORMAL TISSUE BIOPSY

Histology Control

% of cancer and normal cells

MOLECULAR PROFILING

Mutational aberrations

CGH

Transcriptomic Aberrations
WINOTHER concept

Patient with metastatic cancer

TUMOR BIOLOGY & MATCHED NORMAL TISSUE BIOLOGY

Histology Control

MOLECULAR PROFILING

Mutational aberrations

CGH

Transcriptomic Aberrations

% of cancer and normal cells

1. Novelty: use of matched normal and tumoral biopsies from strictly the same patient.

2. Goal is to assess the genetic distance between tumor and normal by profiling of mRNAs
WINThER concept

3. Genetic distance converted into drugs scoring

Computational tools – Algorithm and genes_drugs database

Individual Drug efficacy Scoring Statement

Doctor’s decision
3. Genetic distance converted into drugs scoring
### Example of WINother predictive scoring, that ranks drugs depending on estimated efficacy

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Target Genes</th>
<th>Target Genes List</th>
<th>Found Targets</th>
<th>Found-Targets List (with fold-changes)</th>
<th>Avg Abs (FC)</th>
<th>Avg Abs (FC) UP-REG</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAPATINIB</strong></td>
<td>16</td>
<td>AKT1 BIRC5 CCND1 CCNE1 CDK2 CDKN1B EGF EGFR ERBB2 EREG ESR1 MAPK1 MAPK3 MCL1 PI3KCA PTEN</td>
<td>8 (6+2) (50.0%)</td>
<td>BIRC5 (27.83) CCNE1 (6.54) CDK2 (3.76) EGFR (3.28) EREG (115.04, 201.24) MCL1 (2.14) EGFR (-3.01) ERBB2 (-2.38, -7.62)</td>
<td>26.21</td>
<td>33.62</td>
<td>1260</td>
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<tr>
<td><em>(Tykerb, Tykerb)</em></td>
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<tr>
<td><strong>GEFITINIB</strong></td>
<td>59</td>
<td>ABCG2 ADORA1 AKT1 AREG AVEN CASP3 CDKN1B CGRF1 COL4A3BP CORO1C CYP1A2 CYP2C19 CYP2C9 CYP2D6 CYP2F1 CYP3A4 CYP3A5 DUSP3 DUSP9 E2F1 EGFR EGFR EPOR EPS15 ERBB2 EREG ESR1 FGFR6 GADD45A GADD45G GARS GCLC GNB2 GUCY2D HBEGF IFI6 IGFBP3 IL8 LEPR MAPK1 MAPK3 MLH1 NFKB1 NPTX2 NRL OSMR PARP1 PHLD2 PLBD1 PTEN PTGS2 QSOX1 RBA7 RPA1 Sfn SKI TGFa TNERF1 F1 TUMS</td>
<td>19 (12+7) (32.2%)</td>
<td>AREG (6.33) AVEN (2.50) CASP3 (2.18) DUSP3 (3.90) E2F1 (12.40) EGFR (3.28) EREG (115.04, 201.24) IL8 (32.15) OSMR (6.56, 2.18, 4.28) PHLD2 (19.39, 17.03) PTGS2 (3.62, 3.65) TUMS (6.13)</td>
<td>16.01</td>
<td>21.10</td>
<td>429</td>
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<tr>
<td><em>(Iressa, Irressat, Tarceva)</em></td>
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<tr>
<td><strong>BEVACIZUMAB</strong></td>
<td>1</td>
<td>VEGFA</td>
<td>1 (1+0) (100.0%)</td>
<td>VEGFA (5.33, 3.42, 2.38)</td>
<td>3.71</td>
<td>3.71</td>
<td>371</td>
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<tr>
<td><em>(Avastin)</em></td>
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<tr>
<td><strong>PEMETREXED</strong></td>
<td>10</td>
<td>DHFR FAS FPGS GART GGH RBM17 SLC19A1 TP53 TYMP TUMS</td>
<td>7 (6+1) (70.0%)</td>
<td>DHFR (5.82, 6.73, 12.17, 11.07, 2.11) FPGS (2.53) GART (2.17, 2.39, 2.38) GGH (4.63) TYMP (2.34, 2.79) TUMS (6.13)</td>
<td>4.00</td>
<td>4.29</td>
<td>257</td>
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<td><em>(Alimta)</em></td>
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<td><strong>IMATINIB</strong></td>
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<td>4EBP ABCB1 ABCG2 ABL1 AKT1 ALDH2 ALDOC BCL2L1 BCL2L11 BCR BIRC2 BIRC5 CASP8 CBL CCNA2 CCND3 CDK9 CDCKC CDK4 CFLAR COL1A1 CRK1 CSF1R CUL1 DDR1 DEDD2 EIF4B1 EIF4E FADD FBXO16 FDXW4P1 FGFR3 FRAP1 HDCC HMOX1 1G1H IL2RA KIT LCK LYN MAPK1 MAPK3 MTO1 NFKB1 NTRK1 PDGFB PDGFRa PDGFRb PDHb PPARG PRKCD RB1 RELA RET RPS6KB1 TNFRSF1B VEGFA WTI</td>
<td>26 (14+12) (44.8%)</td>
<td>ABL1 (2.86) ALDOC (2.12) BCL2L1 (2.19) BIRC5 (27.83) CBL (4.24) CCNA2 (13.93) CD69 (3.10) CDCKC (2.38) CSF1R (4.39) HMOX1 (15.13) IL2RA (60.40, 12.30) RPS6KB1 (4.96, 2.10) VEGFA (5.33, 3.42, 2.38)</td>
<td>7.71</td>
<td>9.06</td>
<td>218</td>
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<tr>
<td><em>(Gleevec, Glivec)</em></td>
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WINther study
Main components
WIN THER Participants

Cancer Centers

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

- MD Anderson Cancer Center [USA]
  Lia Tsimberidou, 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
  WIN THER Data Analysis

Worldwide Innovative Networking in personalized cancer medicine
Recruitment goals

Enroll 200 patients with metastatic cancer

Tumor and matched normal tissue biopsies from each patient

Histology Control

Next Generation Sequencing
(mutational and CNV aberrations)

Actionable DNA aberrations
Est. 30-40% of patients

WINThER ARM A:
Patient matched with
existing targeted
therapies or included in
Phase 1 trials

NO Actionable DNA aberration
Est. 60-70% of patients

WINThER ARM B:
Choice of therapy guided by WINThER
drug efficacy predictive scoring derived
from
tumor vs. normal RNA investigations
Estimated repartition of patients

200 patients

Arm A: 80 patients
- Labeled Targeted Therapies: 20 patients
- Targeted Therapies in Clinical Trials: 60 patients

Arm B: 120 patients
- Standard of care: 20 patients
- Off label drugs (non clinical trials): 100 patients
WINther study main objectives

WINther Arm A:
Better identification of actionable DNA aberrations in patients (today limited to 30%), by using NGS
PFS2/PFS1 > 1.5 in 50% of patients

WINther Arm B:
Offer a solution guided by each patient’s individual biology to the vast majority of patients without actionable DNA aberrations

Prove the efficacy of using alternative investigations based on functional genomics of the RNA on a dual biopsy of tumor and matched normal tissue to identify relevant aberrations in patients
PFS2/PFS1 > 1.5 in 40% of patients
Statistical design of the study

Objective of WINTHEIR:
- achieve 1.5 ratio in 50% of patients in arm A
- achieve 1.5 ratio in 40% of patients in arm B
- 30% being the average oncologist threshold
WINATHER Workflow

- Multi-disciplinary trial

Max 6 working weeks
WINOTHER Study
Initial achievements
Recruitment

Rapid Accrual
Currently 2-3 pts / week
From April 16 to July 2, 2013

32 Consents

5 Screening Fails

1 pt included in another therapeutic clinical study
1 pt with rapid worsening condition
1 pt withdraw consent
2 pts with normal tissue not obtainable

8 biopsies yet to be performed

19 Biopsies

7 Logistical Failures

1 inappropiate choice of normal tissue
6 Tumor tissues < 60% of T cells

19 Biopsies

9 Analyzed

IGR-1011 Breast cancer
IGR-1012 Oral squamous cell carcinoma
IGR-1013 Colon cancer
IGR-1016 Lung ADK
IGR-1019 Kidney cancer
IGR-1027 Oral squamous cell carcinoma
Patients characteristics

- Head and neck: 6
- Breast: 5
- Lung: 7
- Sarcoma: 5
- Kidney: 7
- Colon/rectum: 2
WIN oux

Percentage of Cells

NGS + CGH

Not reliable

% of cells

0%
10%
20%
30%
40%
50%
60%
70%
80%
90%
100%

tumor cells

normal cells
WINOTHER

9 sent

8 reports

ARM A

DNA structural alterations
N=5

ARM B

Transcriptomic alterations
N=3

N=5

N=3
Target characteristics

DNA alterations

<table>
<thead>
<tr>
<th>Gene</th>
<th>Mutation</th>
<th>Deletion</th>
<th>Amplification</th>
<th>Gene fusion</th>
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</table>

Transcriptome-based targets

- MET
- VEGFA
- HER3
DNA structural alterations  
N=5

- FGFR1 amp ➔ Included in EOS-3810 study
- HER2 amp ➔ Still on 1st line chemo
- MET amp ➔ On screening (MET inhibitor)
- TSC1 mut ➔ On everolimus therapy
- RET gene fus ➔ On sorafenib therapy

transcriptomic alterations  
N=3

- Target MET ➔ On screening
- Target VEGF-A ➔ Still on treatment
- Target HER-3 ➔ On screening
**IGR-1004**  Head & Neck SCC  
FM: MDM2 ampl, P53 mut  
**BGU:** MET  
**ARM B**  
1/ SAR125844 (Met inhibitor)  
2/ cabozantinib

**IGR-1006**  uterine Leiomyosarcoma  
FM: TSC1 mut  
**ARM A:** Everolimus

**IGR-1007**  Lung ADK  
FM: KRAS G12D  
**BGU:** HER3, HER2  
**ARM B**  
1/ MM-141 phase I  
2/ capecitabine + trastuzumab

**IGR-1010**  Lung Carcinosarcoma  
FM: RET transl, MYC ampl  
**ARM A**  
1/ sorafenib  
2/ switch to another RET TKI with better IC50
IGR-1001  Breast carcinoma  FM: FGFR1 ampl, FGF3 ampl, FGF4 ampl  
   ARM A: lucitanib phase I

IGR-1002  Head & Neck SCC  FM: HER2 and EGFR ampl  
   ARM A: Paclitaxel + Trastuzumab

IGR-1005  Lung ADK  
   FM: EGFR and MET amp  
   ARM A: SAR-MET trial

IGR-1014  Kidney cancer  
   FM: VHL mut  
   BGU: VEGFA  
   ARM B: bevacizumab
Summary: Why is WINTHER different?

- Includes all patients, with or without actionable genetic aberrations
- Investigates both DNA and RNA
- Includes a variety of different technologies: Next Generation Sequencing, Copy Number Variations, gene expression, Comparative Genomic Hybridization
- Based on a dual biopsy of tumor and matched normal tissue of same histology, which enables:
  - Evaluating the genetic distance between tumor and normal
  - Disregarding variability factors between individuals
  - Limiting the number of irrelevant aberrations and noise
  - Increasing the statistical factor of the study by 16
Thank you

Gustave Roussy:
- Fabienne Dufour, Maud Ngo Camus
- Aurélie Abou Lauverne
- Catherine Richon
- Nathalie Auger, Valerie Kouby, Ludovic Lacroix
- Philippe Vielh
- Thierry De Baere
- Gilles Vassal