WINcHER: An International Precision Medicine Trial Incorporating Genomics and Transcriptomics


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Worldwide Innovative Networking in personalized cancer medicine
Disclosures

Dr. Razelle Kurzrock has the following disclosure information: Stock and Other Equity Interests (IDbyDNA, CureMatch, Inc., and Soluventis); Consulting or Advisory Role (Gaido, LOXO, X-Biotech, Actuate Therapeutics, Roche, NeoMed, Soluventis, and Pfizer); Speaker’s fee (Roche); Research Funding (Incyte, Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, Grifols, Konica Minolta, DeBiopharm, Boehringer Ingelheim, and OmniSeq [All institutional]); Board Member (CureMatch, Inc).
AIM:
Increase the number of patients with advanced malignancies receiving a personalized therapy

Patients with advanced solid tumors with no therapeutic option left

Dual Biopsy of Tumor (metastasis) and Normal tissue correlate

Tumor Next Generation Sequencing (FoundationOne)

Differential Expression mRNA Tumor & Normal (Agilent dual color)

WINther Algorithm

No actionable oncogenic alteration

No actionable oncogenic alteration

Actionable oncogenic alteration

Arm A
Therapy based on DNA

Arm B
Therapy based on transcriptome

Response assessment

WINther International Trial over 5 countries
NCT01856296
Study objectives and Sample size

PFS 1
- Standard therapy
- Tumor Progression

PFS 2
- WINTHER oriented therapy
- PFS1
  - > 1.5

200 patients:
- 60 in Arm A
- 140 in Arm B

Statistics
- 92% power to test the improvement rate of Arm A being better than 30% by the exact binomial test with a one-sided 5% type I error.
- 78% power to test the improvement rate of Arm B being better than 30%.
Clinical Management Committee (CMC)

- Convened via weekly teleconference with PIs of the study
- Reviewed FoundationOne NGS and RNA reports
  - First, the CMC determined potentially actionable DNA alteration
  - If there was no potential match, the patient was assigned a drug or drugs based on the RNA report
- Therapeutic decision was also based on factors such as drug/clinical trial availability and patient co-morbidities
- The treatment final decision was made by the treating physicians

Arm A
Therapy based on DNA

Arm B
Therapy based on RNA
Methods - Transcriptomics on Matched Tumor and Normal Tissues

Gene Expression direct comparison of tumor and normal tissue RNAs using Agilent ink jet printing 8x60k oligo-arrays and dual color technology

WINTHER knowledge database based on literature and Cyto-Toxicity Database (http://ctdbase.org) lists the genes shown to be deregulated or in relation with drugs for chemotherapeutic and targeted agents approved, not yet approved or investigational

WINTHER algorithm
A score for each drug essentially based on the percentage of deregulated genes among the target genes for each drug in the tumor sample from the patient.

WINTHER RNA report scoring all drugs by presumed efficacy for each patient
→ Higher scores presumed to be better in terms of therapeutic efficacy.
<table>
<thead>
<tr>
<th>Examples of Primary Tumor Type</th>
<th>Normal matched tissue</th>
<th>Type of normal tissue biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung</td>
<td>Bronchial mucosa</td>
<td>Fibroscopy for normal tissue</td>
</tr>
<tr>
<td>Colon</td>
<td>Rectal/colic mucosa</td>
<td>Rectal/colonoscopy</td>
</tr>
<tr>
<td>Breast</td>
<td>Normal breast tissue</td>
<td>Interventional radiology or echography</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>Skeletal muscle</td>
<td>Interventional radiology or echography</td>
</tr>
<tr>
<td>Head and Neck</td>
<td>Tongue, normal tissue depending on tumor type</td>
<td>Surgery and interventional</td>
</tr>
</tbody>
</table>

Enables control of individual RNA expression variability
Total: 303 patients enrolled
5 consent withdrawals
Patients Characteristics

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>(n=298)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>160 (54%)</td>
</tr>
<tr>
<td>Female</td>
<td>138 (46%)</td>
</tr>
<tr>
<td>Age at inclusion</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>57</td>
</tr>
<tr>
<td>Range</td>
<td>28-84</td>
</tr>
<tr>
<td>Number of prior treatment lines</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>1-12</td>
</tr>
<tr>
<td>&gt; 5 prior treatment lines</td>
<td>27 patients (25.2%)</td>
</tr>
</tbody>
</table>
WINTHER Consort Diagram

303 patients consented

253 patients with dual biopsy tumor & normal correlate

158 patients with treatment recommendation from the Clinical Management Committee (CMC)

124 patients treated

107 patients evaluable treated according to CMC recommendations (35.3%)

69 patients treated in Arm A (DNA) (64.5%)

38 patients treated in Arm B (RNA) (35.5%)

(i) Lesion that could not be biopsied, (ii) Health deterioration, (iii) Death, (iv) Consent withdrawal

Lack of biopsy quality

Health deterioration or death

17 not treated in keeping with CMC recommendations

Without transcriptomics, only about 23% (rather than 35.3%) of consented patients would have been treated. Most prior studies of genome-guided therapy have been hindered by low matching rates, often in the range of ~10% to ~25%.

Attrition rate & slow accrual due to stringent sample requirements for transcriptomics (cellularity & integrity of RNA)

Delay in US regulatory approval could not be compensated by Europe due to time and budget constraints

35.3% patients treated

200 patients planned to be treated: 100 in North America, 100 in Europe, Israel.
## Outcome data including SD >6 months, PR/CR and PFS2/PFS1

<table>
<thead>
<tr>
<th></th>
<th>Arm A (DNA)(^a)</th>
<th>Arm B (RNA)(^a)</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SD &gt; 6 months/ PR/CR(^b)</strong></td>
<td>16 (23.2%)</td>
<td>12 (31.6%)</td>
<td>28 (26.2%)</td>
</tr>
<tr>
<td><strong>Response: CR/PR</strong></td>
<td>9 (13.0%)</td>
<td>3 (7.9%)</td>
<td>12 (11.2%)</td>
</tr>
<tr>
<td><strong>SD &gt;6 months</strong></td>
<td>7 (10.1%)</td>
<td>9 (23.7%)</td>
<td>16 (15.0%)</td>
</tr>
<tr>
<td><strong>PD or SD&lt;6 months(^a)</strong></td>
<td>53 (76.8%)</td>
<td>26 (68.4%)</td>
<td>79 (73.8%)</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>69 (100%)</td>
<td>38 (100%)</td>
<td>107 (100%)</td>
</tr>
</tbody>
</table>

**Frequency (N (%))\(^c\)**

<table>
<thead>
<tr>
<th><strong>PFS2/PFS1 &gt; 1.5</strong></th>
<th><strong>Yes(^d)</strong></th>
<th><strong>No</strong></th>
<th><strong>Total</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>14 (20.3%)</td>
<td>55 (79.7%)</td>
<td>69 (100%)</td>
</tr>
<tr>
<td>No</td>
<td>10 (26.3%)</td>
<td>28 (73.7%)</td>
<td>38 (100%)</td>
</tr>
</tbody>
</table>

**Benefit rate in Arm A and Arm B is equivalent**

**Primary objective of study was not met:**
- ARM A: PFS2/PFS1 >1.5 in 50% of patients
- ARM B: PFS2/PFS1 >1.5 in 40% of patients

**Issues/questions raised:**
- Over-optimistic goal
- Heavily pre-treated patients
- Difficulty to obtain drugs

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\(^a\) Patients who died or whose tumors clinically progressed before the first evaluation were considered as having progressive disease (PD).

\(^b\) *P* values of patients with SD>6months/PR/CR not significantly different between the two arms (two-sided Fisher’s exact test, *p* = 0.37).

\(^c\) Of the 17 enrolled not evaluable because CMC recommendations was not followed, PFS2/PFS1 > 1.5 was 18%; PFS2/PFS1 >1.3 was also 18%.

\(^d\) *P* values of patients with PFS2/PFS1 >1.5 were not significantly different between the two arms (two-sided Fisher’s exact test, *p* = 0.48).
Blinded post hoc analysis performed using a matching score to judge the quality of the therapeutic match based on the drug actually given to patients.

**Arm A (genomics):** number of alterations impacted by the drug(s) administered divided by the total number of alterations.

**Arm B (transcriptomics):** calculated as the reciprocal of the rank of the WINTHER score rank.

Kaplan-Meier curves of various factors influencing PFS and OS

**Arm A**
- PFS by Cancer Site for Arm A
  - Others (E/N = 50/52)
  - Lung (E/N = 16/17)
P-value = 0.0204

- PFS by PS at Treatment for Arm A
  - PS=1 (E/N = 47/48)
  - PS=0 (E/N = 19/21)
P-value = 0.0002

**Arm B**
- PFS by Age Group for Arm B
  - ≤60 (E/N = 20/21)
  - >60 (E/N = 15/17)
P-value = 0.051

- PFS by Sex for Arm B
  - Male (E/N = 25/26)
  - Female (E/N = 10/12)
P-value = 0.0252

- PFS by Number of Prior Treatment for Arm B
  - >2 (E/N = 27/27)
  - ≤2 (E/N = 8/11)
P-value = 0.0096
Kaplan-Meier curves of various factors influencing PFS and OS

PFS2 by PS at Treatment for All Patients

PFS2 by Number of Prior Treatment for All Patients

PFS2 by Number of Prior Treatment for All Patients

OS by Prior Treatments

OS by Matching Score
Kaplan-Meier curves of PFS and OS by matching score and performance status

Panel (a): Progression-Free Survival On Trial (PFS) for Arm A with matching score.
- Matching Score Low (E/N = 19/19)
- Matching Score High (E/N = 47/50)
- P-value = 0.008

Panel (b): Progression-Free Survival On Trial (PFS) for Arm B with matching score.
- Matching Score Low (E/N = 8/8)
- Matching Score High (E/N = 27/30)
- P-value = 0.16

Panel (c): Progression-Free Survival On Trial (PFS) for All with matching score.
- Matching Score Low (E/N = 27/27)
- Matching Score High (E/N = 74/80)
- P-value = 0.002

Panel (d): Overall Survival for All with matching score.
- MS low, PS1 (E/N = 19/19)
- MS low, PS0 (E/N = 9/9)
- MS high, PS1 (E/N = 50/52)
- MS high, PS0 (E/N = 24/28)
- P-value = 0.0002

Panel (e): Overall Survival for All.
- MS low, PS1 (E/N = 18/19)
- MS low, PS0 (E/N = 8/8)
- MS high, PS1 (E/N = 47/52)
- MS high, PS0 (E/N = 14/28)
- P-value < 0.0001

Panel (f): Overall Survival for All.
- Others (E/N = 71/79)
- MS high, PS0 (E/N = 14/28)
- P-value < 0.0001
Effect of individual variability of normal VEGFA RNA expression on assessment of VEGFA levels in tumors
Patient (NSCLC): ARM A

- 72 year-old woman, NSCLC progressing after erlotinib and pemetrexed
- NGS report: EGFR T790M mutation which leads to resistance to the drugs available at the time
- CMC recommended EGFR inhibitor afatinib and EGFR antibody cetuximab (Osimertinib – EGFR inhibitor targeting $EGFR\ T790M$ – was not yet approved)
- Treatment for 13 months beginning in January 2015 and achieved a complete response (CR)
Patient (CRC): ARM A

- 68 year-old man with progressive metastatic colorectal cancer progressing after Xelox (capecitabine and oxaliplatin) and FOLFIRI (folinic acid, 5-fluorouracil, irinotecan) - cetuximab
- NGS report: $MSH6$ mutation (mismatch repair gene alteration causing micro satellite instability)
- CMC recommended pembrolizumab according to data newly emerging at the time (and later validated) regarding checkpoint inhibitor efficacy in a mismatch repair gene defect setting
- Pembrolizumab initiated on March 2015.
- Outcome refers to PR (PFS>36 months)
### Patient (neuroendocrine tumor): ARM B

- 69 woman with a well-differentiated neuroendocrine tumor arising from the small gut with peritoneal metastasis
- Previous treatment: debulking surgery, treatment with lanreotide from April 2011 to June 2012.
- Developed bowel obstruction due to peritoneal progression that requested surgery.
- Somatostatin analog continued until April 2014 when progression to the liver occurred.
- Axitinib (CT) was given for 10 months before progression.
- Was enrolled in WINTHER in April 2015
- NGS report: No DNA alteration
- RNA report: overexpression of *AKT2* and *AKT3*
- CMC recommended treatment included an mTOR inhibitor. Everolimus was started in May 2015
- Achieved prolonged disease stabilization that continues at 34+ months (still on treatment in January 2019)
- Everolimus was later approved for this indication in 2016.

Baseline  

2 years  

3 years
Publications / Presentations


- ASCO 2014 Lia Tsimberidou, Richard L.Schilsky, Alexander Eggermont presentation of personalized medicine trials in the world.. WINTHER

- ASCO 2018 J Rodon. WINTHER

- ESMO 2019 Benjamin Solomon. SPRING 01 – under review
Conclusions

- PFS2/PFS1 did not meet the primary objective
- Using transcripтомic data in a clinical setting is feasible to inform therapeutic choice
- Dual biopsies accepted by patients and no co-morbidities
- WINTHER increased by 35% the number of patients treated in a personalized way based on the unique molecular features of their tumor.
- Overall survival was 25.8 months when patients were adequately matched to a specific treatment using DNA information or WINTHER algorithm vs 4.5 months when treatment matching was not possible (when best matched drug was not available for instance).
- Higher degrees of DNA and RNA matching correlated with higher response rates, and longer progression-free and overall survival.
ONGOING – SPRING 01 IND clinical trial Phase I/II - NCT03386929 - IND 131601

First trial investigating a triple therapy combination for metastatic/advanced non-small-cell lung cancer (NSCLC) in first line of treatment.

Highlights:
- Use of DNA, mRNA and MIR investigations
- Use of a biopsy of both Tumor and Normal tissue (to account for variation in transcription levels)
- Use of the integrative SIMS* algorithm

Thank you to our patients and their families

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WINHER: one of the last projects of WIN Consortium late Chairman, Dr. John Mendelsohn

Foundation Medicine
Agilent
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