WINHER
A study to select rational therapeutics based on the analysis of matched tumor and normal biopsies in subjects with advanced malignancies

Interim trial results

Global investigator coordinator: Pr Jean-Charles Soria

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Data analysis as of May, 19th 2015
Disclosure information

Jean-Charles Soria has received compensation from:

Abbvie, Amgen, AstraZeneca, BMS, GSK, Lilly, Merck-Serono, Merus, MSD, Pfizer, Pierre Fabre, Roche-Genentech, Sanofi, Servier, Symphogen
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Outline

- Rationale
- Design
- Results
  - Trial activation
  - Recruitment
  - Sample processing
  - Patients’ characteristics
- Conclusions
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Standard precision medicine approach

- 40% to maximum 60% of patients’ tumor display a genomic aberration that can potentially get a personalized therapy with a 30% to 90% response rate

- The rest of the patients receive standard therapy
WINThER – aims at increasing the number of patients receiving a personalized therapy

- Tumour biopsy
- Structural DNA changes
- If DNA driver, ad hoc targeted therapy
- Matched normal tissue biopsy
- Transcriptomics
- Therapy based on mRNA transcriptomic profile

By allowing comparative transcriptional profiles with Normal tissue
Why using a Normal tissue biopsy for analyzing the transcriptome?

- Studies have used RNA expression unsuccessfully due to:
  - High level of noise induced by genetic background mixed with tumor specific expression abnormalities

- Matched normal-tumour biopsy allows to:
  - Eliminate noise and variability between individuals
  - Hypothesize that the bigger the “genetic distance” in a gene, the higher the probability that a drug targeting this gene will be efficient
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Study design

- Multicenter: 2 in France, 1 in Spain, 1 in Israel, 1 in Canada, 2 in USA
- Total of 200 treated patients
- Duration of trial: 3.5 years
  - 2.5 years for recruitment
  - 12 months for treatment
  - Follow-up until progression or death
Study objectives

- Primary objective

- Improve the overall performance of the predictive method and fine tune the algorithm.

- Optimize use of biopsies, and increase knowledge in handling biopsies of tumor and normal tissues and optimize histological preparation and extraction of DNA and RNA from strictly the same tumor or normal cells.

- Secondary objectives
WINther workflow

DNA Tumor

Tumor & Normal

RNA Tumor & Normal

NGS

Actionable oncogenic alteration?

Yes

Arm A Therapy based on DNA

No

Arm B Therapy based on transcriptome

Tumor and matched Normal tissue
A multi-step process with many key-steps

1. **BIOPSIES**
   - Only Normal available
     - Or only Tumor available
     - **FAILURE**
     - STOP
   - Normal + Tumor
     - If < 50% tumor cells in tumor tissue
       - **FAILURE**
       - STOP
     - New biopsy of tumor tissue
       - Restart the whole procedure
     - If ≥ 50% tumor cells in tumor tissue
       - DNA & RNA extraction / quality control
         - If only DNA
           - Or only RNA
             - DNA\(^1\) + RNA\(^2\)
             - Send DNA to FM
             - Send RNA to GR
             - Only 1 report available
           - **FAILURE**
           - New biopsy
             - STOP
             - FM + BGU report
             - Review at CMC
             - STOP
         - **FAILURE**
   - **FAILURE**
   - **FAILURE**

1. DNA is extracted from tumor tissue
2. RNA from normal and tumor tissues
Study Participants

Recruiters

Europe
- Gustave Roussy
- Vall d’Hebron Institut d’Oncologia

Middle East
- The Chaim Sheba Medical Center at Tel Hashomer - Est. 1948
- The Hospital of Israel

Americas
- Segal Cancer Centre at the Jewish General Hospital

Other centers yet to recruit
- Centre Léon Bérard Lyon et Rhône-Alpes
- UC San Diego Moores Cancer Center
- MD Anderson Cancer Center
- Foundation Medicine
- Agilent Technologies
- Ariana Pharma

1st patient included June, 17th 2015
Outline

• Rationale

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  - Sample processing
  - Patients’ characteristics

• Conclusions
Trial activation

- **Protocol development**
  - Logistics
  - Funding

- **Recruitment of key players**

**Project development**

- **September**
  - Initiation of protocol design
  - Grant submission to EU
- **April**
  - Protocol approved by WIN
  - Funding from EU granted
- **July**
  - Protocol submissions started
  - First site activated
  - First patient recruited

**Project implementation (from protocol submission to activation)**

- **2012**
- **2013**
  - Activation of Sheba
  - Activation of VHL
  - Activation of GRCC
- **2014**
  - March
  - Activation of McGill
- **2015**
  - April
  - July
  - 250 patients enrolled
  - Full regulatory approval for MDACC and UCSD

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## Trial activation cont.

<table>
<thead>
<tr>
<th>Site</th>
<th>Time from protocol submission to IRB approval</th>
<th>Process for Health Authority approval</th>
<th>Total time from concept to activation</th>
<th>Total time from concept to first patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gustave Roussy Cancer Center (France)</td>
<td>1 month</td>
<td>1 month</td>
<td>19 months</td>
<td>19 months</td>
</tr>
<tr>
<td>MD Anderson Cancer Center (USA)</td>
<td>36 months</td>
<td>~ 16 months</td>
<td>36+ months</td>
<td>Not yet achieved at 56+ months</td>
</tr>
<tr>
<td>UC San Diego Moores Cancer Center (USA)</td>
<td>36 months</td>
<td>~ 16 months</td>
<td>36+ months</td>
<td>Not yet achieved at 56+ months</td>
</tr>
<tr>
<td>Vall d'Hebron Institute of Oncology (SPAIN)</td>
<td>1 month</td>
<td>2 months</td>
<td>22 months</td>
<td>22 months</td>
</tr>
<tr>
<td>Oncology Institute at the Chaim Sheba Medical Cancer (ISRAEL)</td>
<td>6 months</td>
<td>4 months</td>
<td>22 months</td>
<td>22 months</td>
</tr>
<tr>
<td>Segal Cancer Center, MCGill University (CANADA)</td>
<td>9 months</td>
<td>1 month</td>
<td>30 months</td>
<td>30 months</td>
</tr>
</tbody>
</table>

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Recruitment

Accrual

Number of patients

Recruitment cont.

Origin of patient recruitment

- Gustave Roussy: 42%
- VHIO: 23%
- Chaim Sheba: 22%
- Segal CC: 13%
Study update

Inclusion
- 250 patients included
- 4 Withdraw consent

Biopsy
- Tumor and normal biopsies available for 185 patients
- 38 screen failures before biopsy (normal: 6; tumor: 19; not medical: 2; other: 11)

Treatment decision
- 100 treatment decisions
- 70 failures after biopsy
  - 45 related to tumor tissue
  - 18 to normal tissue reasons
  - 7 degradation/death before CMC

Treatment start
- 46
- Arm A n = 29
- Arm B n = 17
- 24 will not start treatment
  - 13 degradation/death after CMC,
  - 11 other: decided to pursue other treatment, contraindication to Winther treatment

Waiting for biopsy (n= 23)
Waiting for Treatment decision (n= 15)
Waiting for Treatment start (n= 30)
A multi-step process with many key-steps and gate keepers

BIOPSIES

Only Normal available Or only Tumor available

Normal + Tumor

If ≥ 50% tumor cells in tumor tissue

DNA & RNA extraction / quality control

If only DNA Or only RNA

DNA\(^1\) + RNA\(^2\)

Send DNA to FM Send RNA to GR

New biopsy of tumor tissue

STOP

FAILURE (26%)

STOP

FAILURE (50%)

New biopsy of tumor tissue

Restart the whole procedure

FAILURE (12%)
Biopsy site

**Tumor tissue biopsy site**

- LIVER: 80 patients
- LUNG: 50 patients
- Not available: 40 patients
- LYMPH NODES: 20 patients
- HEAD AND NECK: 10 patients
- GI TRACT: 10 patients
- OTHER: 30 patients

**Normal tissue biopsy site**

- RECTAL/COLIC MUCOSA: 60 patients
- Not available: 50 patients
- BRONCHIAL MUCOSA: 40 patients
- NORMAL BREAST TISSUE: 30 patients
- HEAD AND NECK: 20 patients
- GI TRACT: 10 patients
- OTHER: 20 patients
The highest failure rate for normal tissue was observed in normal breast (83%) due to the high content in adipose tissue.
Hurdles linked to biopsies and quality controls

High level of heterogeneity in tumor sample preventing macrodissection

K: number of biopsy; Black:Tumor
Blue: Non tumoral tissue; Green: Necrosis/Hemorrhage/Fibrin; Red: µm scale
Drastic reduction of failures with sites’ improved performance

- Overall failures decreased from 71% to 30%

- Biopsy related failures decreased from 39% to 15%

% failure related to tissue procedures by study period (all centers)

Training is essential
Data web portal to support weekly Clinical Management Committee of all PIs in 5 different countries
Patients' characteristics

<table>
<thead>
<tr>
<th></th>
<th>Frequency N=246*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>131 (53%)</td>
</tr>
<tr>
<td>Female</td>
<td>115 (47%)</td>
</tr>
<tr>
<td><strong>Age at inclusion (years)</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>56</td>
</tr>
<tr>
<td>Range</td>
<td>25 ; 82</td>
</tr>
<tr>
<td><strong>Nr. of previous treatment lines</strong></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>3</td>
</tr>
<tr>
<td>Range</td>
<td>1 ; 16</td>
</tr>
</tbody>
</table>

* 4 patients withdrew their consent and are not counted in the analysis
Patient’s tumor diagnosis

- **LUNG** 24%
- **COLON** 20%
- **BREAST** 14%
- **GI TRACT** 12%
- **HEAD & NECK** 11%
- **KIDNEY** 4%
- **OTHER** 11%
- **Not available** 4%
Timeline from biopsy to treatment decision

Fresh tumor Biopsy + Pathological control

Molecular screening NGS-Gene Expression

Clinical Management Committee (CMC)

Treatment

Median: 61 days (7 weeks)

Range: 35 to 434 days
Conclusions

- Matched tumor/normal tissue biopsies have proven to be:
  - Acceptable by patients and feasible in some tumor types
  - Safe

- Use of frozen biopsies and a 60% tumor cellularity threshold for transcriptomic investigations remains a complex logistical challenge

- FFPE could alleviate that challenge
Conclusions cont.

- Clinical Management Committee (CMC) weekly web conference of all PIs and support portal with all data is a key achievement.
- Weekly Laboratory teleconferences and mutual training were instrumental to achieve failure rates decrease.
Conclusions cont.

- For patients, who had passed the stringent quality controls, we were able to **provide a personalized treatment decision (n=100)** based on either genomic or transcriptomic information.

- Regulatory agencies need to be brought along early on in the design of future breakthrough trials such as WINTHER to avoid any delay in opening of the trial.
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Thank you for your attention