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Highlights from the WINTHER Trial

A study published in the May 2019 issue of Nature Medicine demonstrates for the first time in the clinic that transcriptomic (RNA expression testing) can be used to tailor precision medicine in oncology to a greater number of patients based on the increased expression of RNA in tumors compared to normal tissues. Agilent gene expression microarrays were used in this study. Below are highlights from this study.

Genomic and transcriptomic profiling expands precision cancer medicine: The WINTHER trial (NCT01856296)

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Purpose

Expand precision oncology to patients with advanced solid tumors that progressed after treatment with standard therapies.

About the study

– 303 patients were enrolled in WINTHER trial; 107 of whom were ultimately treated according to recommendations made by a committee of cancer experts spanning five countries. These patients had been heavily pretreated, with one quarter having received five or more prior lines of therapy. Of the 107 patients treated, 69 received treatment based on DNA mutation profiling, and 38 based on RNA profiling. Overall, the WINTHER trial succeeded in matching personalized therapy to 35% of patients with advanced cancer.

– In this trial, patients were first evaluated for targetable alterations in cancer driver genes. Those who were not matched to drugs based on DNA alterations received a treatment tailored to the differences in gene expression between patients' tumors and normal tissues which were assessed using a patented algorithm developed by the WIN Consortium. **Agilent's unique 2-color gene expression analysis enabled the study which needed to compare tumor and normal tissue of same patient.** This feature proved to be essential due to highly variable RNA expression between patients and across normal tissue types. The WINTHER researchers showed that RNA expression can be used to expand personalized therapy options for patients, providing an additional 10% proportion of patients treated.

– Patients who received therapy optimally tailored to their respective DNA alterations, or consistent with the algorithm recommendation for RNA guided treatment, responded better. Patients with a good performance status and a high degree of matching had a significantly longer median overall survival of 25.8 months versus 4.5 months for others.

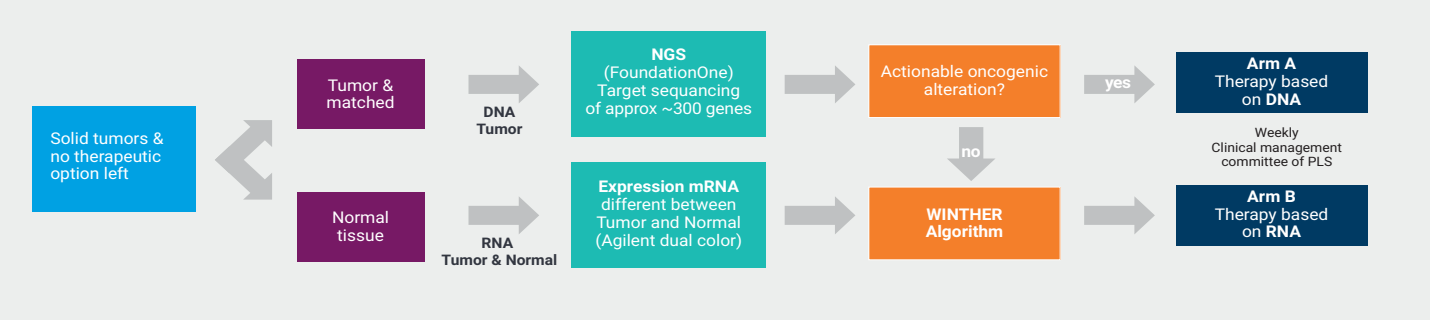


Figure 1. Schematic summary of Winther trial workflow.

Highlights

The WINTHER trial is unique, as it included several novel paradigm shifts, here summarized:

– **Inclusion of transcriptomic information, in addition to genomic profiling, to help patients with various solid tumors to get access to a larger panel of therapies.**

– Using a NGS gene panel of 236 genes, rather than less comprehensive testing, for the genomic arm (Arm A).

– Timely CMC teleconference discussions that included investigators from centers in France, Spain, Israel, Canada and the United States.

– Navigating patients to a clinical trial or to on-label approved or off-label-approved drugs.

Strategy and WINTHER algorithm

In order to translate gene expression data into actionable therapeutic decisions, they have developed a novel strategy and algorithm. The analysis developed is based on three main pillars:

– Dual biopsies to discard most genetic variability between individuals (analysis of gene expression and miRNA profile assessment in tumor vs normal tissue of same patient).

– A knowledge database (standard-of-care and investigational drug information included).

– An innovative algorithm that enabled linking the patients RNA information to a knowledge database and provided a ranked drug list for each patient.

What researchers say

"The strategy employed on WINTHER resulted in a higher proportion of patients treated than in many precision medicine trials. Previous studies have identified potential treatments for between 5% and 25% of patients based on DNA profiling alone, findings represent an important step toward delivering on the true promise of precision medicine in oncology"

Richard L. Schilsky, Chairman WIN Consortium and Chief Medical Officer of ASCO

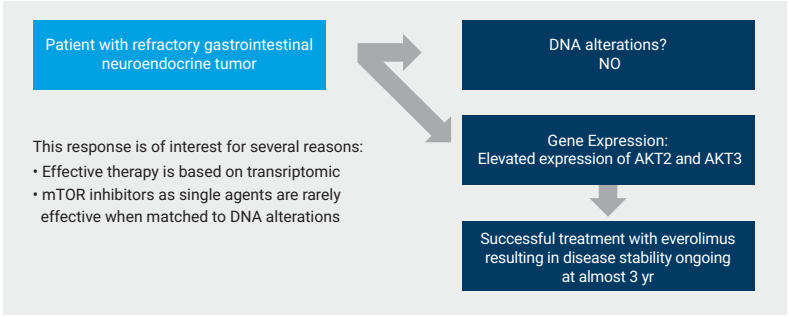
"Importantly, our results show that patients treated with a drug or regimen more closely matched to the molecular profile of their tumor, do better"

Razelle Kurzrock, co-leader of the WINTHER trial and Director of UCSD Moores Center for Personalized Cancer Therapy

"Assessing RNA is an important adjunct to DNA profiling for determining precision treatments. WINTHER rings in a new era for personalized medicine in oncology"

Josep Tabernero, Vice-Chairman WIN Consortium, Director VHIO and President ESMO

Case of interest



Conclusions

The WINTHER trial integrated a new generation of genomic and transcriptomic tools in a decision-making process considering patient therapy options at an individual level, depending on the characteristics of each person's tumor.

For the first time in the clinic, the WINTHER trial applied transcriptomics (RNA expression testing) to tailor precision medicine in oncology to a greater number of patients based on the increased expression of RNA in tumors compared to normal tissues.

Transcriptomics increased the percentage of patients who could be administrated matched therapy and successfully navigated 35% of patients with refractory cancers to therapy.

Link to abstract: **https://www.nature.com/articles/s41591-019-0424-4**

WIN Consortium webpage: **http://www.winconsortium.org/clinical-trial/winther-trial1**

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PR7000-2316

Printed in the USA, September 25, 2019
5994-1367EN

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