WIN Consortium Applies Transcriptomics to Bolster Patient Matching in Precision Oncology Study

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CHICAGO (GenomeWeb) – The combination of DNA and RNA analysis allowed more cancer patients to be matched to precision medicine options than would have been possible based on DNA analysis only, a study presented at the American Society of Clinical Oncology's annual meeting showed.

Although the WINTHER study, conducted by the WIN Consortium, did not meet a prespecified clinical benefit endpoint, a blinded, post-hoc analysis showed that when patients received treatments they were most likely to benefit from, as determined by high matching scores, they lived significantly longer compared to those who did not get the top-matched therapies. The WINTHER investigators said the data demonstrate the importance of integrating transcriptomics into precision oncology trials alongside DNA analysis.

In the WINTHER study, conducted by the WIN Consortium, 35 percent of 303 consented advanced cancer patients matched to a treatment. First, patients were tested for targetable alterations in cancer genes using Foundation Medicine's FoundationOne test. Those who weren't matched to targetable drugs based on detected genetic alterations had another shot at getting matched to a treatment based on the differences in gene expression in the tumor and normal samples (assessed by microarrays). Without the RNA-based algorithm, the match-rate would have been 23 percent.

"One of the issues with precision medicine trials has been the low matching rate," Razelle Kurzrock, co-leader of the WINTHER trial and director of the Center for Personalized Cancer Therapy & Clinical Trials Office at the University of California, San Diego's Moores Cancer Center, told GenomeWeb. However, the match-rate seen in WINTHER is high for a precision medicine trial, she said, given that most other studies have placed between five percent and 25 percent of patients on to treatment arms after DNA profiling.

"As there are more drugs available and people gain more experience, and in particular, by adding transcriptomics, we are increasing the percentage of patients matched," Kurzrock said.

The aim of the WINTHER study was to use transcriptomics to try to bolster the number of patients receiving personalized therapies. Out of 303 consented patients, ultimately 107 patients were

treated, 69 based on DNA profiling and 38 based on RNA profiling.

Although a high match rate is often touted as demonstrating the success of the precision oncology paradigm, it ultimately has little value unless patients benefit from the treatment to which they were matched. And in WINTHER, there were a number of difficulties that kept researchers from recruiting the number of patients originally planned and from meeting the study's primary endpoint.

Researchers had aimed to enroll 200 patients — 60 in arm A where patients were tested by FoundationOne and 140 in arm B where patients were matched based on transcriptomics — from America, Europe, and Israel. "Back when we designed this trial, we thought that we would find actionable results in a minority of patients [in arm A,] and that most patients would be treated in arm B," said Jordi Rodon from MD Anderson Cancer Center while presenting the data.

However, the trial was unable to recruit the requisite number of patients in the US due to regulatory delays and funding limitations.

Moreover, researchers set a high bar for themselves in terms of the benefit they wanted patients to experience in the study. They decided to compare the progression-free survival patients had to matched therapies in WINTHER (PFS2) against the progression-free survival they had to the therapy prior to joining the trial (PFS1).

The expectation generally is that with each cancer progression patients will derive less and less benefit from later lines of treatment. "The idea is if PFS2 can be equal to PFS1 then disease is stable," said Vladimir Lazar, chief scientific and operating officer of the WIN Consortium and an investigator on WINTHER. "But if PFS2 is longer than PFS1, then you've reversed the tendency of incrementally worse outcomes on subsequent lines of treatment and that shows a clinical benefit."

The patients recruited to WINTHER were heavily pretreated, with 25 percent having had more than five prior lines of therapy. But the investigators had hoped to demonstrate that even such heavily pretreated, advanced cancer patients would benefit more from matched treatment compared to the prior line of therapy. In this regard they hoped to show a PFS2 to PFS1 ratio of greater than 1.5 in 50 percent of patients in arm A and in 40 percent of patients in arm B.

The PFS2/PFS1 ratio "is a powerful way [of showing treatment benefit] because every patient serves as his or her own control," said Lazar, but he noted that the goal in WINTHER to show a ratio greater than 1.5 was far too ambitious when a ratio of greater than 1.3 is well accepted and has been used in prior precision oncology studies, such as MOSCATO.

In WINTHER, this prespecified endpoint was ultimately reached in only 20 percent of patients in arm A and in 22 percent of patients in arm B.

Eddy Yang from the University of Alabama at Birmingham reviewed the WINTHER data at the meeting and commended the investigators for setting a higher bar in terms of the PFS ratio. He noted though that while the PFS ratio "eliminates that variability between patients" when evaluating the benefit of treatment, there are also downsides to using this endpoint. "There are a lot of other factors that can influence this ratio," he said, such as the prior and current treatment given to the patient, whether the previous PFS was measured accurately, and the differences in prognosis between tumor types.

Yang recognized that the increase in the match rate from 23 percent to 35 percent using

transcriptomics is significant in that it represents perhaps the highest match rate in a precision oncology trial. The match rate reported in WINTHER, however, was exceeded by another precision oncology study called i-PREDICT, which also released data at the meeting.

In that study, also led by Kurzrock, researchers from the University of California, San Diego, MD Anderson Cancer Center, and elsewhere enrolled approximately 150 advanced cancer patients using the FoundationOne test to gauge 315 genes, and if possible, based on tumor mutational burden, circulating tumor DNA, and PD-L1 status by immunohistochemistry. They reported being able to match 73 patients, or nearly 50 percent, to a targeted drug or immunotherapy combination.

"I think what's happening, is that precision oncology trials are getting better," Kurzrock said, though she maintained that to the best of her knowledge WINTHER has the highest match rate based on the published data from precision oncology trials. While there was an abstract on i-PREDICT at ASCO, it has not been published on.

Despite the high match rate, the biggest challenge within WINTHER was garnering sufficient tumor content in samples to enable RNA analysis. Although 253 out of 303 consented patients agreed to provide tumor and normal samples, only 158 patients received treatment recommendations based on their FoundationOne results and transcriptomic analysis, largely due to difficulties with procuring sufficient tumor samples for RNA analysis.

Rodon noted that for transcriptomic analysis the sample quality requirements were much more stringent and required 50 percent tumor content. "The consensus is building that RNA is actually very important," Kurzrock said. But because RNA has been more difficult as far as getting adequate samples and processing, she said that not many in the research community have included RNA analysis in precision oncology studies.

In WINTHER, each site had to learn how to process the samples for transcriptomics, but the sites got better at doing this as they gained experience, recalled Kurzrock. In subsequent WIN Symposium trials, researchers hope to avoid the attrition rates seen in WINTHER by using paraffin-embedded samples, which can be microdissected to increase the tumor content.

Another difficulty in WINTHER was with access to drugs. Based on the literature and the Comparative Toxicogenomics Database (a repository of chemical–gene/protein interactions), WIN has amassed a database of genes that are deregulated in cancer and which influence drugs response and resistance. Using this database, researchers are able to identify the targetable genes that are deregulated in each patient's tumor and apply an algorithm to rank the drugs that they might benefit from most.

Patients who matched to an approved or investigational drug based on this algorithm were enrolled in arm B. But Kurzrock estimated that only around 50 percent of patients received the top ranked drug according to DNA and RNA matching.

A clinical management committee reviewed DNA and RNA test results from study participants, but ultimately made recommendations based on patient's comorbidities and whether a particular drug or trial was available at a specific institute or country. "We ranked more than one option for patients, and we discussed with the physician the range of options," Kurzrock said. "And we tried to give the best option considering the reality that existed for that patient."

The reality for many patients in WINTHER, though, was that they didn't get the top treatment option

according to molecular testing. So, researchers conducted a post-hoc analysis to evaluate how patients fared when they did receive drugs based on a high matching algorithm for both arms A and B.

"We thought this was very important to do because if patients were not well matched, we wanted to know if that made a difference when they were highly matched versus poorly matched," Kurzrock said, emphasizing that this was a blinded analysis to avoid bias.

For arm A, researcher devised an algorithm — dividing the number of genomic alterations matched by the total number of characterized DNA alterations — to determine which patients got a high matching score. For arm B, they used the RNA algorithm. When investigators compared all treated patients with good performance status and a high matching score against everyone else, the median overall survival was 25.8 months versus 4.5 months, respectively. "This contains an important lesson in that if you give a better matched drug, patients do better," Kurzrock said.

Following Rodon's presentation at the meeting, some oncologists in the audience commended the investigators for using transcriptomics to guide therapy choice, and in particular analyzing gene expression in tumor versus normal samples. Others at the meeting were more reserved in their judgement.

"Doing a transcriptional analysis, looking at that set of drugs, we're not ready yet," said another oncologist from the audience. "Sequencing every patient, it's negligent as an oncologist to do that in advanced cancer patients, not because we can match all patients but because we can match very few as you said. That's evolving at a rapid rate, but to try to push that too hard and talk about effective personalized medicine actually doesn't help the field."

Rodon responded that WINTHER was a learning opportunity and the WIN collaborators are proceeding carefully. The study, for example, only matched patients based on RNA data when they failed to match to a therapy using FoundationOne. Additionally, despite the challenges the study faced in procuring samples with high tumor content, it was apparent that patients are willing to give tumor and normal samples from molecular analysis.

"I'm not saying that on the basis of this one trial transcriptomics can become the standard of care, but the trial definitely suggests that transcriptomics should be an important part of additional clinical trials," Kurzrock said, noting the need for further studies.

The follow-on study to WINTHER will be SPRING, which will investigate the safety and efficacy of giving advanced lung cancer patients a triplet therapeutic strategy based on a biomarker algorithm that matches patients to the combinations. This algorithm incorporates targeted genomic sequencing, copy number variation, transcriptomics, and miRNA expression, and patients will have their normal and tumor tissue analyzed.

Kurzrock reflected that genomic and transcriptomic testing are very rapidly evolving technologies. While some may feel that these tools aren't ready to used broadly in cancer care, "there is more and more evidence, and to me it's pretty compelling evidence, that genomics and now transcriptomics is important for precision medicine trials," she said.

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