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## FDA Okays WIN Consortium Trial to Test Three-Drug NSCLC Combo; Validate SIMS Algorithm

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### **Premium**

NEW YORK (GenomeWeb) – The US Food and Drug gave its blessing this week to launch a trial that will investigate the safety and efficacy of three targeted drugs and validate a biomarker algorithm for identifying which advanced non-small cell lung cancer patients will benefit from the combination.

The so-called Survival Prolongation by Rationale Innovative Genomics (SPRING) trial has been designed by the WIN Consortium, a network of academic medical centers, drugmakers, and diagnostics companies, payers, and patient advocates across 17 countries. The SPRING trial will be conducted at eight WIN sites in various countries, including the University of California, San Diego's Moores Cancer Center, Avera Cancer Institute, Institut Curie, Centre Léon Bérard, Hôpital Paris Saint-Joseph, Vall d'Hebron Institute of Oncology, Centre Hospitalier de Luxembourg, and Chaim Sheba Medical Center.

In the study, researchers will test out the triple-therapy approach, a strategy that has successfully reduced viral load in AIDS patients, making it a chronic disease. Investigators led by Razelle Kurzrock, senior deputy director for clinical science at UCSD's Moores Cancer Center, are hypothesizing that three targeted therapies with different modes of action will be able to achieve what targeted single agents have failed to do so far in precision oncology, especially in lung cancer — stave off cancer resistance and prolong long-term survival.

The three-drug combo initially being investigated in the SPRING trial are two treatments developed by Pfizer, Ibrance (palbociclib) and Inlyta (axitinib), and a third, Bavencio (avelumab) codeveloped by Pfizer and Merck KGaA. Ibrance is a CDK4 and CDK6 inhibitor. Inlyta is anti-angiogenic drug that blocks c-KIT, VEGF receptors, and PDGFR, while Bavencio is an immunotherapy that targets PD-L1.

Lung cancer treatments over the past 50 years haven't worked for patients, Kurzrock said in an interview, because "we were blindly throwing drugs at [them] hoping something will stick." Around 14 percent of NSCLC patients with Stage IIIA disease are alive five years after diagnosis; with stage IIIB disease the five-year survival rate is 5 percent. When the disease has spread to other parts of the body, the five-year survival rate drops to 1 percent.

The field is only starting to make headway in improving outcomes in lung cancer, Kurzrock said, by following the science, embracing the complexity of disease, and understanding the uniqueness of the patient. But precisely because cancer is complex, giving patients one matched therapy doesn't make much biological sense, Kurzrock reflected. "We need more than one drug in order to accomplish what we're trying to accomplish," which is to cure patients.

The triplet strategy in oncology is being explored by others. In a mouse model, researchers led by Antonio Ribas tested the combination of a BRAF inhibitor, MEK inhibitor, and an anti-PD1 drug in melanoma and observed a "superior antitumor effect" and manageable toxicity. They [wrote](#) in *Science Translational Medicine* in 2015 that their findings support testing this triple combination in patients with BRAFV600E mutant metastatic melanoma.

"What the science is telling us is that patients are complicated. We have to look at patients as individuals, we have to understand that tumors are complicated, and we have to develop combination [treatments] that make sense for those individuals," Kurzrock continued. "We [also] have to have tools with which we can measure what's going on in the tumor. Fortunately, we have those tools now in the form of genomic and transcriptomic assays."

In Phase I of the SPRING trial, researchers will explore the safety of this combination in a small number of patients and establish dosing. The efficacy of the three-drug combination will then be tested in a Phase II trial as a first-line option in advanced NSCLC.

Since around 20 percent of patients with tumor alterations in EGFR, ALK, ROS1, and MET already have targeted treatment options, they can't enroll in the study. SPRING is aiming to be an option for the majority of advanced NSCLC patients who currently lack precision treatment options. Researchers will collect blood and tumor samples from patients, and retrospectively test the ability of the so-called simplified interventional mapping system (SIMS) to identify which patients respond best to the triplet therapy.

Brandon Young at Avera WIN Precision Oncology Laboratory in California will analyze patients' biopsies using an Illumina NGS platform and HTG Molecular's EdgeSeq mRNA and miRNA expression panels. Then, Eitan Rubin at Ben-Gurion University of the Negev in Israel will integrate the data within the SIMS algorithm to identify best responders.

In a 2015 *Oncotarget* [paper](#), Kurzrock and colleagues described how they developed SIMS by analyzing lung tumor and normal tissue using targeted genomic sequencing and also looking at copy number variation, transcriptomics, and miRNA expression. Using these techniques, they identified 24 "interventional nodes" that were driving cancer but could also be targeted by drugs, and developed a scoring system to rank how disturbed these nodes were. Based on which nodes were co-activated, Kurzrock's group defined triplet therapies for overcoming resistance.

The three-treatment regimen "is based on what we know about the biology of lung cancer, that there is a subset of patients that match, at least from the pre-clinical work, really well with these drugs," Kurzrock said. "We're going to be able to use our assays to see if the subsets that we predicted would really do respond."

Based on input from the FDA, Kurzrock and colleagues will test out SIMS retrospectively first and then prospectively in later-stage studies. Researchers expect that SIMS will identify a larger subset of enrolled patients as having biomarkers that allow them to benefit from at least one drug in the triplet regimen, and a smaller subset to have biomarkers that enable benefit from all three.

While SPRING is getting off the ground studying this first triplet, Kurzrock added that WIN is negotiating adding second triplet combo soon. WIN's goal is to ultimately study six triplet combinations that would offer options for more subsets of NSCLC patients and elucidate the ability of SIMS to match patients to the

right combinations. "SIMS will start to make sense when you have six combinations," said Vladimir Lazar, chief scientific and operating officer at WIN.

With all six triplets in play, Lazar envisions using SIMS to generate a profile of all the therapeutic possibilities for a patient. "We estimate that each patient will have more than one therapeutic option," he said, which would allow NSCLC patients to switch to different combinations as resistance emerges and extend survival for many more years than currently possible.

In choosing Ibrance, Inlyta, Bavencio as the first test of WIN's three-drug strategy, it helped that Inlyta and Bavencio have [already been studied](#) in combination and there were not red flags in terms of additive effects of the combination. The safety profile of each drug also suggests that they don't appear to overlap in terms of toxicity, noted Lazar.

But the difficulty with studying what Kurzrock calls "rational combinations," guided by tumor biology, toxicity profiles, and other patient characteristics, is that multiple drug developers will have to collaborate. "Honestly, that's a big challenge," she acknowledged. "That's one of the reasons all three of these drugs involve the same company."

Although Pfizer is involved in the development of all three drugs being studied in SPRING, at least one drug in this regimen was codeveloped with Merck. Lazar commended Pfizer and Merck for having the vision to evaluate their drugs as part of a triplet combination, but he acknowledged that most drug developers may not yet be ready to work with competitors to study rational combinations in the kind of new paradigm WIN wants to advance.

Running precision oncology trials combining one targeted therapy and a test that analyzes one or two genes is already challenging in terms of aligning the interests of drug and diagnostic makers. But enough companies have attempted such Rx/Dx alliances that a playbook of best practices has started to emerge. For WIN, there was no historical example to guide its efforts to study three drugs and integrate an algorithm that relies on a range of biomarkers.

"This is a very big achievement that an entity like WIN could pass all the barriers and put all the forces together to place the patient at the center," said Lazar.

However, this first triplet combination will be the proving ground for getting other drugmakers to join in. "There's nothing like success that can motivate people," Kurzrock reflected. "Drug companies are driven by a profit motive, but there are a lot of people who work at drug companies who'd really like to see they're making a big impact on the lives of cancer patients."

There is certainly potential for substantial profits from the successful commercialization of a triplet regimen involving drugs each priced at around \$10,000 or more a month (the wholesale price of Bavencio is \$13,000/month without payer discounts.) Although the costs will undoubtedly increase when more drugs are added to a regimen and when extensive molecular analysis is required, that's not the right parameter to look at from a health economics standpoint, Kurzrock said. "The cheapest thing is for the patient to die," she noted.

WIN conducted an informal analysis that showed that the cost per life year of a patient went down, when he or she received the right therapy, one that extends survival and provides for good quality of life. "There is nothing more expensive than what we do a lot of in the clinic now, [which] is give very expensive drugs to the wrong patients, and it doesn't help them, and a lot of times it makes them worse."

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