

# Reactive Oxygen Species May Have Antitumor Activity in Metastatic Melanoma

By Rabiya S. Tuma

An investigational drug that causes cells to produce excess reactive oxygen species (ROS) was associated with unexpectedly long progression-free survival in a small trial of patients with metastatic melanoma. The drug's mechanism of action, the trial design, and the trial outcome are all unusual in the field, but just how important they will be remains an open question, according to experts.

In the phase II trial, 81 patients with metastatic melanoma were randomly assigned to receive either paclitaxel plus the ROS-inducing agent elesclomol (formerly STA-4783) or paclitaxel alone. Patients taking elesclomol had a median progression-free survival of 3.7 months, compared with 1.8 months for those in the control arm—a statistically significant difference. Moreover, 35% of patients were progression free in the combination arm at 6 months versus 15% in the control arm.

"I think it is the first—in terms of randomized and placebo controlled—study in metastatic melanoma" to show improved progression-free survival, said Stephen O'Day, M.D., chief of research and director of the melanoma program at the Angeles Clinic and Research Institute in Santa Monica, Calif., who led the trial.

If these data are replicated, researchers will have two reasons to celebrate: the identification of both the first effective agent for melanoma in decades and a drug with a relatively untried mechanism of action. Biologists know that ROS can be

toxic to cells, are abundant in cancer cells, and can sometimes trigger programmed cell death (apoptosis). But this finding would be some of the first clinical evidence that a compound that increases the amount of ROS in cancer cells can kill them.

ROS, such as hydrogen peroxide, are natural by-products of normal cellular metabolism. Cells have evolved enzyme systems to convert these dangerous chemicals into benign ones, but the systems can be overwhelmed or damaged. When that happens, ROS accumulate in the cell and can damage proteins, lipids, and nucleic acids. Although extensive damage, or damage to critical features of the cell, may trigger cell death, many cells can tolerate and repair the occasional hit from ROS.

When the balance tips further in favor of ROS, however, programmed cell death becomes a near certainty, according to John Fruehauf, M.D., Ph.D., associate professor of clinical medicine at the University of California at Irvine Chao Family Comprehensive Cancer Center. Excess ROS, which the cellular enzymes cannot neutralize, alters the chemical environment within the mitochondria. Once that happens, a pore protein that forms a channel through the mitochondrial membranes becomes jammed in the open position, allowing cytochrome *c* to escape into the cytoplasm of the cell. Once free of the mitochondria, cytochrome *c* is a well-known instigator of programmed cell death. Because cancer cells already have excess ROS because

of their abnormal metabolic activity, researchers have hypothesized that tumor cells are more sensitive than healthy cells to drugs that disrupt ROS cleanup. This supposition may be particularly true in melanoma, in which melanin synthesis also releases ROS. In vitro and preclinical data with elesclomol and other ROS-disrupting agents seem to support that hypothesis.

Scientists have known for many years that the mitochondria must keep strict control of ROS, but the full details of how the components of that system, cell signaling, and programmed cell death fit together have only recently become clear.

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John Fruehauf, M.D., Ph.D.

Elesclomol appears to induce the production of ROS by activating an intracellular enzyme (Synta Pharmaceuticals, maker of elesclomol, declined to provide more specific information about which enzymes may be activated). Several other investigational agents currently in clinical trials act by blocking ROS cleanup.

"If [this mechanism] sensitizes the cancer cell to other forms of mitochondrial cell death, which other chemotherapy agents act through, this would be a nice common mechanism we've been looking for in oncology," O'Day said.

For example, Fruehauf is testing a combination of the chemotherapy drug temozolomide and an experimental agent called ATN-224 in a phase II trial in patients with

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metastatic melanoma. ATN-224 inhibits a key enzyme required for ROS inactivation, and temozolomide damages DNA. And because both excess ROS and DNA damage can trigger apoptosis, the combination may be lethal to cancer cells, Fruehauf said. Healthy cells can tolerate the excess ROS and, in theory, will survive the ROS onslaught. Elesclomol also seems to increase the activity of many standard chemotherapy agents *in vitro*, which may support that hypothesis.

### Interesting Trial Design

The elesclomol trial is also interesting because there are few good ideas for new melanoma drugs. O'Day acknowledges that the trial is small, which could be problematic, but he said they need to try something new in melanoma.

"For 30 years, we have nothing to show in terms of rigorous randomized trials, and some of the problem has been that we do these small, single-arm studies. You see a few good outcomes—and melanoma is a very heterogeneous disease—and then they launch these huge 700-patient trials and they are all negative. So here the whole goal was to pick an endpoint that was stricter than response rate, meaning progression-free survival, and do a randomized, placebo-controlled trial."

In addition to the experimental arm's success in progression-free survival, eight patients (15%) in the experimental arm had an objective response—compared with just one (3.8%) in the control arm. The researchers also found that patients on the combination therapy survived longer than those taking paclitaxel alone: 12.0 months in the experimental arm versus 7.8 months in the control arm. However, overall survival was not a predetermined endpoint in the trial, and patients were allowed to cross over to the experimental arm after disease progression on single-agent paclitaxel.

While melanoma researchers agree in general that using randomized phase II trials is a move forward for the field, some individuals think that the specifics of the elesclomol trial were cause for concern

and may increase the likelihood that the subsequent phase III trial will fail. For example, the trial design called for a 2:1 randomization scheme, so 53 patients were assigned to the experimental arm and 28 to the control arm. That means a small control arm in a disease that, as O'Day himself said, is different from patient to patient.

However, that's not a reason to disregard the trial, said Edward Korn, Ph.D., of the biometric research branch at the National Cancer Institute, who has been studying past melanoma trials to find historical benchmarks. "If they had just shown us the one experimental arm with the 53 patients, no one would believe any of this

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because you can really fool yourself if you happen to get a good group of patients. I think it is more convincing [as randomized trial], but I wish they had made it two to three times larger."

Melanoma researchers have also raised concern about an imbalance between the two arms in the proportion of patients with M1c disease. These patients, who are known to have poorer overall survival, made up 75% of the patients in the control arm, compared with 53% in the experimental arm. That difference could tip the trial in favor of the experimental arm, according to Keith Flaherty, M.D., assistant professor of medicine at the University of Pennsylvania in Philadelphia.

O'Day noted that in a small phase II trial there are bound to be some imbalances like this one. The trial investigators

did not stratify patients that way because M1c disease is not associated with differences in progression-free survival, which was the primary endpoint of the trial. It is associated with poorer overall survival, which the trial did not initially aim to measure.

The near-complete lack of responders in the control arm also sparks concern for Flaherty. "That is not what we think paclitaxel does by itself in melanoma. It gives you the sense that there is something wrong with that control arm," he said.

However, the investigators disagree. "I do not understand the comments that the paclitaxel-alone group had particularly poor performance," said Alexander Eggermont, M.D., Ph.D., head of surgical oncology at the University Hospital Rotterdam-Daniel den Hoed Cancer Center in The Netherlands, who is the primary investigator for the European portion of the phase III trial with elesclomol. "On the contrary: It had standard performance." In a recent phase III trial, patients treated with another single-agent therapy in the control arm had a median 1.6-month progression-free survival, which is similar to the 1.8 months achieved in this phase II trial, he said.

The data are promising enough that GlaxoSmithKline has partnered with the Synta Pharmaceuticals on an international phase III trial designed to enroll 630 patients and test for prolonged progression-free survival and overall survival.

Both Eggermont and O'Day acknowledge that small trials can be misleading. But they say that, thus far, the development of elesclomol has been done using a conservative trial design. And, given the outcome of that early trial, the only thing to do now is to move into a large patient population to see whether the benefit remains.

"Certainly there are still major risks as for whether this will turn out to be a positive phase III trial, but to do a randomized, placebo-controlled trial at this stage of the disease is a step forward," O'Day said.