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New MD Anderson President Ron DePinho on His Evolution as a Physician-Scientist

BY ERIC T. ROSENTHAL

He applied for the job only at the last minute, at the urgings of colleagues, but then soon realized after spending two days interviewing on the Houston campus he had visited many times before in other capacities how much he truly wanted to be president: "I was blown away by the magnitude of talent across all levels of the institution on a clinical level and the amount of resources and the capabilities. The esprit de corps and collaborative spirit offered a unique opportunity, and I knew then that I had to convince the Board of Regents."

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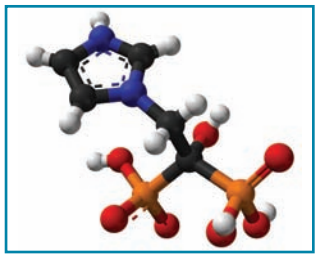

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JOE SIMONE Interviews 4 Oncologists about Their Recent Professional Moves p.5

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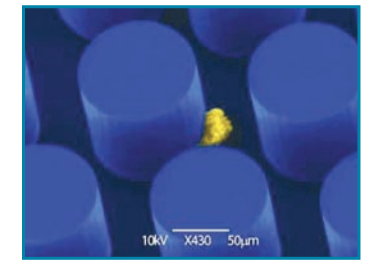
PERIODICALS

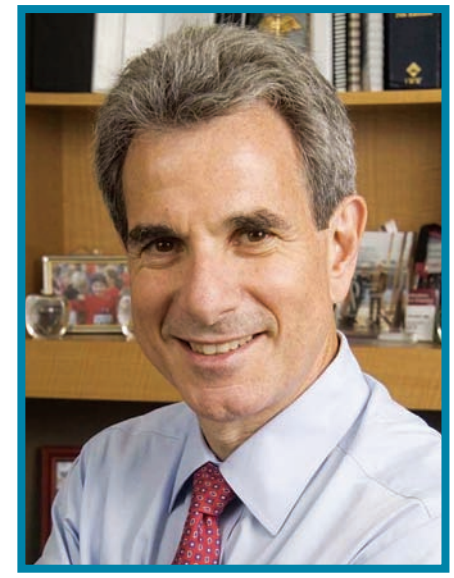
Circulating Tumor Cells Move One Step Closer to Use as Surrogate Trial Endpoint in Prostate Cancer



BY RABIYA S. TUMA, PHD

In the last 15 months, the US Food and Drug Administration has approved three new agents for the treatment of castrate-resistant prostate cancer, and several more agents have shown promising results in late-stage trials. While all of this is good for patients, the prolonged survival provided by the increasing number of active drugs makes future drug development more difficult as long as the primary trial endpoint remains survival.

With that challenge in mind, Howard Scher, MD, Chief of the Genitourinary Oncology Service at the Sidney Kimmel Center for Urologic and Prostate Cancers at Memorial Sloan-Kettering Cancer Center, and colleagues are working to identify a biomarker panel that can serve as a surrogate for survival in Phase III trials and regulatory approval in the future.



HOWARD SCHER, MD: "What we are trying to do is establish a biomarker that can replace survival [as a primary endpoint] in a clinical trial. If we have to keep waiting for people to die, that is not a very efficient way to do things."

Their early results, presented at the ASCO Annual Meeting *(Abstract LBA4517),* suggest that a biomarker panel including circulating tumor cells and baseline LDH correlates closely with survival in a retrospective analysis of a randomized prospective trial. The investigators are now working to refine the panel and validate it in independent trials.

"What we are trying to do is establish a biomarker that can replace survival [as a primary endpoint] in a clinical trial," Dr. Scher said in an interview. "If we have to keep waiting for people to die, that is not a very efficient way to do things."

That point was reiterated by Daniel George, MD, Director of Genitourinary Medical Oncology and Director of the Prostate Clinic at Duke University School of Medicine, who discussed the abstract following Dr. Scher's presentation. "We really need this," Dr. George said. "Clearly we are limited with our intermediate endpoint assessments."

Pain and bone scans are not validated endpoints, RECIST largely ignores tumor burden in bone, and PSA tests do not capture treatment effects, he continued. Without adequate surrogates for survival, trials and new drug approvals will be slowed. "Cumulatively, we've almost doubled the survival of prostate cancer patients with these added therapies over the last couple of years."

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Poetry by Cancer Caregivers

Submissions are welcome from oncologists, oncology nurses, and other cancer caregivers. E-mail only, please, to: OT@LWWNY.com, and include affiliation/title, address, and phone number, along with a photo, if available.

AMIR STEINBERG, MD, is Assistant Professor of Medicine at Tisch Cancer Institute at Mount Sinai Medical Center in New York City, in the hematologic malignancies/stem cell transplantation group in the division of hematology-oncology. He wrote this poem focused on his encounter with POEMS Syndrome, a condition one of his patients has.

When One Thinks of POEMS

BY AMIR STEINBERG, MD

One thinks of the beauty of words
Of iambic pentameter and limericks
Of Shakespeare and of Frost
One does not think of a disease

A syndrome that debilitates
A condition that incapacitates
Any organ system susceptible
And that is what we have

Every nerve may be involved
Endocrinopathy is a concern
Enlarged organs abound
Even monoclonal gammopathy!

Involvement of the skin!
Increased hemoglobin and platelets!
Increased fluid retention!
Increased VEGF!

Ultimately, therapy is difficult
Undermining our efforts,
Understand that POEMS
Usurps the poetry of the human body

→CTCs

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Developing the Marker

To ensure that a biomarker panel would be an acceptable surrogate in a regulatory context, Dr. Scher and collaborators have been discussing the project with the FDA. Moreover, they are using the Veridex CellSearch circulating tumor cell (CTC) assay, which has been analytically validated and shown to be reproducible.

In the current study, the investigators developed and tested the panel using data from the Phase III abiraterone trial. Nearly 1,200 patients were randomly assigned to either abiraterone or placebo in a 2:1 fashion. At a second, preplanned interim analysis, patients in the active drug arm had a statistically significant improvement in median overall survival relative to placebo, at 4.6 months versus 3.9 months.

Abiraterone treatment appeared to benefit patients who had a favorable CTC count (less than 5 cells/7.5 ml blood) at baseline, as well as those who had an unfavorable count (5 or more cells/7.5 ml blood). Moreover, the conversion rate from unfavorable to favorable, which has been shown previously to be prognostic in prostate cancer patients, was higher in the abiraterone arm, compared with the placebo arm after just four weeks of treatment.

When the team looked for characteristics associated with improved survival in a multivariate model, they found that baseline LDH, baseline CTC count, and treatment were all statistically significant variables. PSA was not.

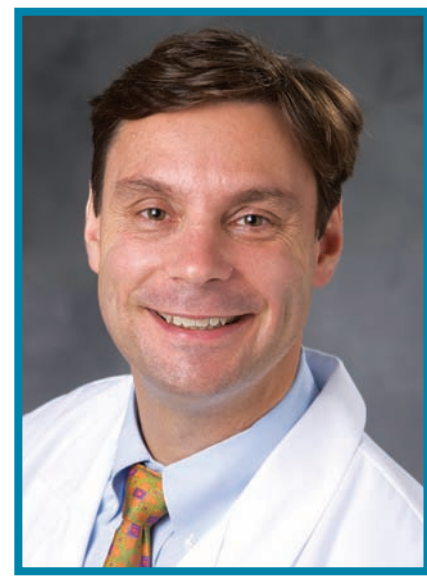
Dr. Scher's group found that a biomarker panel consisting of CTC conversion at week 12 of treatment and baseline LDH was strongly associated with survival. Adjusting for the model in a multivariate analysis attenuated the effect of treatment. Thus the biomarker panel appeared to account for the drug's benefit.

"We understand that capturing the full treatment effect on survival with a biomarker is realistically too high a bar to obtain," Dr. Scher said. "Nevertheless, when we factored in the effect of treatment on survival, after accounting for the biomarker panel, we found that the treatment effect was no longer apparent."

Dr. George was also enthusiastic about the ability of the panel to absorb the treatment effect. "What is interesting with abiraterone and the CTC [panel] is that it does appear to explain all of the treatment effect associated with this drug."

More Work to Be Done

Despite that close correlation, Dr. Scher said that the current biomarker panel is unlikely to be the exact panel the research team will take to the FDA for qualification, which is the term used to indicate that the agency accepts the biomarker's value in a specific setting. The group is continuing to tweak the panel's contents, and are testing its predictive value in other data sets.



Duke Health

DANIEL GEORGE, MD: "What is interesting with abiraterone and the CTC [panel] is that it does appear to explain all of the treatment effect associated with this drug."

Once the team is convinced they have a robust biomarker, they plan to test it in independent, prospectively collected trial data. In fact, investigators have been collecting blood for blinded CTC biomarker testing in three ongoing Phase III trials.

Dr. Scher says that participation by various trial sponsors demonstrates both the need for a surrogate marker, and the community's commitment to developing one.

Not for Guiding Individual Patient Treatment

One thing the biomarker panel is not designed to do is help direct individual patient treatment. "We're not really trying to study a strategy for the individual patient," Dr. Scher said. "What we are really looking to do is develop a trial strategy that will allow accelerated approval of drugs."

He noted that if they wanted to adapt the biomarker panel for individual patient use, they would need to test it in different ways. For example, they would need to show that using the biomarker to guide treatment decisions improved patient outcomes, compared with standard clinical practice.

Dr. Scher serves as a consultant or advisor for both Cougar Biotechnologies, which developed abiraterone, and Veridex, and received honoraria from Cougar Biotechnologies. Dr. George has a working relationship with Johnson & Johnson, which now owns both Veridex and Cougar Biotechnologies. OT