

ONCOLOGY TIMES

Publishing for
31
Years

Lippincott
Williams & Wilkins
Wolters Kluwer
Health

The Oncology &
Hematology Source



Shakeup at CTRC Puts Ian Thompson at Helm

BY ROBERT H. CARLSON

In 2007, when the CTRC merged with the University of Texas Health Science Center at San Antonio, changes in direction caused an exodus of research talent and a drop in philanthropic income. Well-known and well-respected, Dr. Thompson is the CTRC's third new leader in five years. His biggest challenges: regaining what was lost and, perhaps the greatest—getting back the NCI Comprehensive Cancer Center designation lost in 2002, along with a five-year (rather than the current three-year) term as an NCI-Designated Cancer Center.

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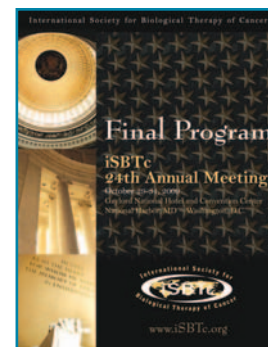
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iSBTc Meeting: Cancer Immunotherapies Moving Closer to Clinical Utility

BY PEGGY EASTMAN



NATIONAL HARBOR, MD—Decades of research aimed at harnessing immune system approaches to fighting cancer are paying off. So said speakers at the 24th Annual Meeting of the International Society for Biological Therapy of Cancer (iSBTc), held at the Gaylord National Hotel and Convention Center here.

Although there have been disappointments clinically along the way, the research is yielding fruit in a number of areas showcased at the meeting, including basic immunology, therapeutic cancer vaccines, adoptive cell transfer, viral and cellular proteomic targets, manipulation of the tumor microenvironment, and cancer and inflammation. In informal conversation with *OT*, several physicians said they believe immunotherapy represents the future of cancer treatment because it promises effective tumor eradication with fewer side effects.



JEFFREY SCHLOM, PHD, noted that a recent 43-center randomized Phase II vector-controlled study of patients with metastatic castrate-resistant prostate cancer showed that the PSA-TRICOM therapeutic vaccine (PROSTVAC) extended survival and that a Phase III trial is expected to start next year.

In his talk, keynote speaker Mark M. Davis, PhD, Professor of Microbiology and Immunology and a Howard Hughes Medical Institute investigator at Stanford University School of Medicine, cited an increased understanding of T-cell recognition as one factor helping to usher in what he termed “the coming golden age of human immunology and immunotherapy.”

Dr. Davis noted that since T-cell recognition is a key event in the development of most immune responses, the use of tumor-specific T cells for cancer immunotherapy makes sense scientifically. His research is

focused in part on T-cell recognition of specific peptide-MHC complexes (a desired outcome for cancer immunotherapies) and on self-antigen reactive T cells—abundant in peripheral blood—and how the immune

system keeps these cells from causing autoimmunity.

“We need to develop a much more extensive knowledge of human immunology, independent of animal models, in order to

correctly navigate the challenges of developing immunotherapies,” he emphasized.

Several speakers said they believe *continued on page 34*

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that immunotherapy—such as therapeutic cancer vaccines—will be most promising clinically when used in combination with other cancer treatments. “Preclinical data have now demonstrated, and clinical data are emerging, on the benefit of combination therapies employing chemotherapy, hormone therapy, small molecule targeted therapy and local radiation with vaccine,” said Jeffrey Schlom,

PhD, Chief of the Laboratory of Tumor Immunology and Biology at the National Cancer Institute.

“Several of these additional therapies, when used in appropriate dose scheduling

regimens, have the ability to enhance host immune function and/or alter the phenotype of tumor cells to render them more susceptible to vaccine-mediated T-cell killing.”

Dr. Schlom also described how thera-

“We need to develop a much more extensive knowledge of human immunology, independent of animal models, in order to correctly navigate the challenges of developing immunotherapies.”

—Mark M. Davis, PhD

peutic vaccine efficacy can be enhanced using poxviral vectors expressing transgenes that encode one or more tumor-associated antigens and three T cell costimulatory molecules (B7.1, ICAM-1, LFA-3), designated as TRICOM. A recent 43-center randomized Phase II, vector-controlled study of patients with metastatic, castrate-resistant prostate cancer showed that the PSA-TRICOM therapeutic vaccine (PROSTVAC) increased patient survival in the treatment group vs. the control group.

He noted that a Phase III trial of this promising therapeutic vaccine is expected to begin in 2010, and PROSTVAC is being developed by NCI and private industry under a Cooperative Research and Development Agreement.

In Combination

Glenn Dranoff, MD, Associate Professor of Medicine at Harvard Medical School and the Dana-Farber Cancer Institute, agreed with Dr. Schlom that immunotherapies might be most effectively used in combination: “Efficacious cancer immunotherapies will likely require combinations of strategies that enhance tumor antigen presentation and antagonize negative immune regulatory circuits,” he said.



NICHOLAS P. RESTIFO, MD, said that in using the technique of adoptive cell transfer, the state of differentiation of anti-tumor T cells before their transfer is critically important for their effectiveness. The realization that “younger” T cells have increased effectiveness in adoptive cell transfer for melanoma immunotherapy points the way overall toward the use of the most appropriate cells for immunotherapy in patients with cancer, he said.

His own research is focused on granulocyte-macrophage based therapeutic cancer vaccines. He has discovered several of the molecular pathways underlying a dual targeting of melanoma cells and the tumor vasculature, a finding that has led him to believe that combining therapeutic anti-cancer vaccines with anti-angiogenic treatments might be a good clinical strategy.

Carl H. June, MD, Director of Translational Research and Professor in the Department of Pathology and Laboratory

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MDS Epigenetic Therapies: New Evidence for Limiting Therapy Duration in Unresponsive Patients

BY RABIYA S. TUMA, PHD

“I think we have a very well-done azacitidine trial in high-risk MDS that shows a doubling of survival at two years, and an increase in median survival in two randomized trials, and decitabine—albeit using a dose schedule most of us don’t use—doesn’t show a survival benefit.”

SAN FRANCISCO—Randomized controlled trial data from earlier this year show that azacitidine prolonged overall survival in patients with high-risk myelodysplastic syndrome (MDS) compared with three standard therapeutic regimens. A question left open in that publication, though, was whether patients with stable disease but no evidence of hematologic response derived a survival benefit from azacitidine. During a review of epigenetic therapies at the Oncology Congress here, one researcher revealed that as yet unpublished data indicate that these patients do not show a survival benefit and can be taken off therapy.

“I can tell you—between you, me, and the walls—that it is my impression of the data, that if a patient doesn’t have hematologic improvement by six months and you decide to stop because you don’t see it benefiting the patient, you can sleep well that night,” said Steven Gore, MD, Professor of Oncology at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins University. “It is probably a reasonable decision. In terms of survival, you are not selling the patient short.”

He made those comments based on his posthoc analysis of the large randomized AZA001 trial. He said the full analysis will be formally presented at the American Society of Clinical Oncology Annual Meeting this spring.

The AZA001 trial met its primary end-

point of overall survival, with the 179 patients in the control arm having a median survival of 24.5 months compared with 15.0 months for the 179 patients in the control arm. The investigators undertook the posthoc analysis to discover whether the survival benefit extended to patients who had stable disease but did not show a hematologic response. According to Dr. Gore, those patients who did not show evidence of hematologic response by the end of six cycles (six months) did not gain a survival advantage with azacitidine therapy compared with standard treatment.

Unlike standard chemotherapy regimens, which work quickly, epigenetic therapies take time to work.

“People who are not showing hematologic improvements after six months, I am personally stopping therapy or switching therapy,” Dr. Gore said. “If the survival of the people who are stable on supportive care is the same or better, then I don’t think there is any reason to spend a lot of money and treat the patient in a way that is not being beneficial to them.”

Wendy Stock, MD, Professor of Medicine at the University of Chicago Medical Center, who chaired the session in which Dr. Gore spoke, declined to comment specifically on Dr. Gore’s unpublished data, but said “What the data suggest, I think, is that if there is no major response by four to six cycles, then there is not going to be. If there is clear evidence of progression, I would take them off before that. There is some discussion that there may be some benefit to stabilization of disease in terms of quality of life, but that remains to be determined.”

A previous analysis of AZA001 data, presented by Lewis Silverman, MD, of Mount Sinai School of Medicine in New York City, at the 2008 American Society of Hematology Annual Meeting, looked at the time to first evidence of hematologic improvement.

Unlike standard chemotherapy regimens, which work quickly, epigenetic therapies take time to work. Fifty percent of the patients who ultimately developed an objective response showed some hematologic improvement by two cycles; by six cycles 87% had done so.

“So if you do what I do and stop drug after six cycles if you don’t see a response, there are a few people who might have gotten a response,” Dr. Gore said. “But if cut off before six cycles you are certainly going to miss some responders.” Based on that analysis and the unpublished analysis, he

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Medicine at the University of Pennsylvania, is using engineered T cells for cancer immunotherapy. “We are exploring the use of engineered T cells bearing chimeric receptors and strategies to augment their anti-tumor efficacy in adoptive transfer settings,” he said.

Specifically, his preclinical research is focused on using lentiviral engineered T cells that incorporate a tumor resistance genotype, which, he said, should have an “improved function for cancer immunotherapy.” This preclinical research is being done in humanized mouse models bearing tumor xenografts; the engineered T cells are able to eradicate large, well-established tumors in these preclinical models,

he noted.

In using the technique of adoptive cell transfer, the state of differentiation of anti-tumor T cells before their transfer is “critically important for their effectiveness,” said Nicholas P. Restifo, MD, an investigator in NCI’s Surgery Branch. Dr. Restifo and his collaborators are focusing on identifying the functional and phenotypic qualities of adoptively transferred T cells that mediate tumor regression in melanoma.

He said that “younger” T cells appear to be more effective, and that these young, undifferentiated T cells must be capable of maturing into fully functional T cells after adoptive transfer.

The realization that these younger T cells have increased effectiveness in adoptive cell transfer for melanoma immunotherapy points the way overall toward the use of the most appropriate cells for immunotherapy in patients with cancer, he said. ☐

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manage information, he said. “Over the last five years, the system has improved significantly.”

Rajiv Datta, MD, Medical Director of the South Nassau Cancer Center and Chairman of the Department of Surgery and Director of Surgical Oncology at South Nassau Communities Hospital in Oceanside, NY, said his staff interviewed about five vendors to see who would have the best support going forward and who could customize a system for surgical oncology.

“We also wanted to make sure that the vendor would be around and available to upgrade the system as time went by.”

Front desk staff and nurses should also be able to directly access system support, and the care team should work with the technical support team to develop a backup

plan in case software crashes, he said, adding that records at his facility are stored off-site on a second server in case of such a problem.

Potential Product Limitations

Dr. Vogel cautioned that despite the many benefits of EHR systems, oncologists do need to be aware of potential product limitations.

Don’t assume that just because an EHR has chemotherapy ordering functions that the product will serve all of the needs of a practice, and practices must also make sure that EHR systems incorporate and access complex data sets and the most recent clinical data, he said.

Moreover, access to genomic information and personalized medicine has not been completely incorporated into the IT models used by commercial clinical and research products. Such features, Dr. Vogel said, will need to be addressed going forward. ☐

