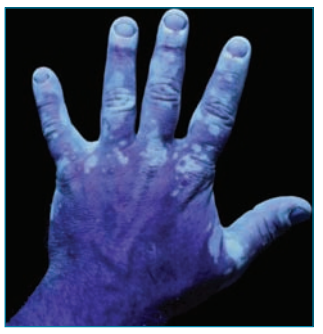
# Melanoma: Immunotherapy-Induced Vitiligo Documented as Linked to Better Outcomes

BY KURT SAMSON

Although it occurs in only a small number of melanoma patients, immunotherapy-induced vitiligo-like depigmentation appears to be a sign of reduced risk of disease progression and increased survival, according to a review of the medical literature published in the *Journal of Clinical Oncology (**2015;33:773-781**)*.

The researchers, from the Netherlands Institute for Pigment Disorders, note that although research specifically addressing vitiligo is very limited, such patients have two to four times less risk of disease progression and death, respectively, compared with patients who do not develop vitiligo from treatment.

The team reviewed data on 5,737 patients with stages III to IV melanoma treated with immunotherapy that had autoimmune toxicity and/or vitiligo between 1995 and 2013. Included were 11 papers on general immune stimulation, 84 on vaccine-associated vitiligo, 28 on antibody-based treatment studies, and 16 on adoptive transfer trials.



The researchers—first author was Hansje-Eva Teulings, MD—found that in 27 studies the cumulative incidence of vitiligo was 3.4 percent and was significantly associated with progression-free melanoma outcomes. In 85 of 139 treatment arms, patients developed vitiligo-like depigmentation on immunotherapy and 304 of 5,737 patients developed vitiligo. Adoptive transfer of cytotoxic T-lymphocyte therapy accounted for most cases (6.3%).

The senior author, Rosalie M. Luiten, PhD, Professor of Dermatology, noted that in a small number of patients, vitiligo-like depigmentation is caused by strong anti-melanoma immunity that also targets healthy melanocytes. One large prospective, hospital-based, observational study found a cumulative incidence of 2.8 percent in 2,954 patients with different stages of melanoma, regardless of treatment.

"Our study shows that the development of vitiligo in melanoma patients receiving immunotherapy significantly correlates with prolonged survival," she said. "Vitiligo is a clinically relevant parameter for the success of immunotherapy in melanoma. This is important

## SUNITINIB/SCLC

*Continued from page 63*

"Despite achieving good disease control initially, patients with SCLC usually experience relapse within six months of first-line chemotherapy and often do not respond to subsequent chemotherapy."

bar for success is lower, or should both limited and extensive stage be included, increasing the relevant population for study and accelerating accrual?"

Because half of the sunitinib subjects in the Ready et al study required dose reduction, she also asked if the next trial should use 25 mg daily instead of 37.5 mg, although lower doses of drugs for other diseases have resulted in decreased effectiveness and the same might prove true for sunitinib.

The editorial also asked if such a study should also include other possible targets of sunitinib. Because the new study did not report activity in other biomarkers, she said she wondered if subjects selected for a Phase III trial should be exclusively chosen for VEGF or if other protein expression, genomic alterations, or other potential predictors of sunitinib benefit, such as genetic polymorphisms or tumor microRNA levels, should be also included.

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"These researchers have successfully completed a challenging Phase II trial, demonstrating a clear signal of benefit with sunitinib. Should they proceed to a larger study? The chance of a successful Phase III trial based on positive Phase II results has been estimated at 28 percent. Will sunitinib be the next advance in the treatment of SCLC or just another blind alley? There is only one way to find out," Leighl concluded.

### Toxicity Concerns

Also asked for his perspective for this article, David R. Spigel, MD, Director of Lung Cancer Research at Sarah Cannon Research Institute in Nashville, Tennessee, said that conducting a Phase III study at this time could well be premature: "I'm a little biased because Dr. Ready and I conducted similar studies, but we stopped ours [***Lung Cancer 2012, 77:359-364***] because the toxicity levels with sunitinib were too high."

In addition, he said, although the new study suggests that sunitinib may increase progression-free survival, this may not translate in a larger Phase III trial: "I am very much in favor of exploring anti-angiogenesis agents and the data so far has been encouraging, but we saw this a few years ago with thalidomide, which also initially showed promise against SCLC tumors but was later found in a larger study to provide no benefit while increasing the risk of blood clots and other serious adverse events."

### Search for Biomarkers

Spigel also emphasized that researchers have yet to identify a biomarker for angiogenesis in tumors and, historically, SCLC trials have generally been negative and selecting a sizeable study population for a larger study would be difficult. Moreover, there is no way to know if the new findings will translate into better overall survival rates over time.

DAVID R. SPIGEL, MD: "The data so far has been encouraging, but we saw this a few years ago with thalidomide, which also initially showed promise against SCLC tumors but was later found in a larger study to provide no benefit while increasing the risk of blood clots and other serious adverse events."

"If a Phase III trial is to be conducted at this point, I think it will take a tremendous leap of faith to do so. We probably need better efficacy data upfront, and there has not been enough of this data in the Phase II studies conducted thus far."

Several researchers are looking at other potential angiogenesis inhibitors that may prove to be better candidates for trials in these patients, he added: "The full story is far from done yet, but we could be getting closer to finding an actual biomarker for these cancers. I am also excited about some of the advances being made in immunotherapy to treat these patients. I personally think that we will have better strategies in the future."

## MELANOMA & VITILIGO

*Continued from page 64*

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### Under-reported?

Luiten noted that many clinical studies fail to report the presence or absence of vitiligo development, so the study may underestimate its frequency in advanced melanoma patients. Also, little is known about the incidence of vitiligo in melanoma patients or the relationship with clinical outcome in general, because most evidence comes from individual studies or case reports.

"We recommend that physicians consider vitiligo when treating melanoma patients and register this information in national melanoma treatment registries. This will enable more precise measurement of the frequency of vitiligo in current and future clinical studies."

Immune-related adverse effects after melanoma immunotherapy have been associated with increased clinical efficacy. Vitiligo-like depigmentation is a relatively harmless type of autoimmunity that can occur spontaneously in patients with melanoma or when they are on immunotherapy.

### Current Prognostic Biomarkers

Current prognostic biomarkers in melanoma are based on the American Joint Committee on Cancer TNM staging system and include Breslow tumor thickness, ulceration, extent of nodal involvement, site(s) of distant metastases, and serum lactate dehydrogenase, all of which are associated with general disease progression and survival.

"Our review shows that the development of vitiligo in melanoma patients receiving immunotherapy significantly correlates with prolonged survival," Luiten said. "This means that vitiligo is a clinically relevant parameter for the success of immunotherapy in melanoma patients. Response-predictive biomarkers to immunotherapy are scarce, and a prognostic factor to evaluate outcomes in melanoma treated with immunotherapy is needed."

ROSALIE M. LUITEN, PHD: "This is important because immunotherapy is currently one of the greatest breakthroughs in cancer therapy. Considering the low response rate of patients to immunotherapy, the priority of the field is finding biomarkers of therapy responsiveness."

She added that the study's limitations are similar to those with any large-scale review of the medical literature—The researchers had to combine survival and vitiligo development data across studies, with outcome definitions that vary across studies. More significant was that the vitiligo was observational and based on the each investigator's level of awareness of vitiligo. Vitiligo was not an outcome parameter in any of the studies.

"No randomized studies and only a few Phase III studies were included because of a lack of grade 1 or 2 autoimmunetoxicity evaluations. The studies described only the absence or presence of any autoimmune toxicity defined as vitiligo negative," she said.

> Awareness of vitiligo induction in patients with melanoma is important as an indicator of robust anti-melanoma immunity."

Moreover, the researchers reported that dermatologists were not typically involved in the studies they reviewed, and it is not clear to what extent oncologists accurately diagnose vitiligo in patients with fair skin types.

### Recommendation to Use Wood's Lamp

The research team recommend that all future prospective immunotherapy studies in patients with melanoma should include complete skin examinations by a dermatologist using a Wood's lamp—a hand-held fluorescent lamp that emits long-wave ultraviolet A light, which delineates areas of pigment loss—both at baseline and other time periods.

"Taken together, our results show a favorable effect of vitiligo induction as a relevant clinical parameter in patients with end-stage melanoma receiving immunotherapy," she said.

Greater awareness of vitiligo induction in melanoma patients by oncologists may help better recognize patients with effective anti-melanoma immunity, and may influence their treatment options and prognosis, she added.

"To draw better conclusions in immunotherapy studies, we recommend the use of the immune-related adverse events criteria and reporting vitiligo systematically on an individual patient data level—in addition to monitoring of immune responses—in future melanoma immunotherapy studies.

WILLIAM SHARFMAN, MD: "In my experience I do not remember any African-American patients developing vitiligo. Most are Caucasian patients, and what they experience is quite striking. So this new information does not change much from my clinical perspective."

### No Surprises

Asked for his perspective, William Sharfman, MD, Associate Professor of Oncology and Clinical Co-director for Oncology at the Johns Hopkins Melanoma Program of Sidney Kimmel Comprehensive Cancer Center, said he was not surprised at the findings, which have been known for some time.

"What is surprising is that so few patients develop the condition," he said. "Even with the most active therapy, only about two percent of patients develop the skin condition, and I believe that figure is more accurate. I did not find the paper terribly helpful. It was a review of earlier trials, not an actual analysis of new research."

His areas of clinical expertise include cutaneous oncology, dermatology, gastrointestinal cancers, and immunotherapy, and he helped create the Johns Hopkins Melanoma Program in 1994.

He said the incidence of vitiligo is not becoming more common, and said he does not think that vitiligo helps prospectively predict who will get the disorder or what their risk actually might be.

"It is an interesting phenomenon, though. If treatment is killing melanocytes, the incidence of vitiligo in general is lower than expected, but I do not know that this new data helps quantify the effect or choice of treatment."

He added that is to be expected that rates would be lower in African-Americans because they have naturally higher melanin content in their skin.

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