Tremelimumab Doesn't Live Up to Standard Chemo

BY NEIL OSTERWEIL
Contributing Writer

CHICAGO — Add tremelimumab monotherapy to the list of treatments that showed potential for improving metastatic melanoma survival but have failed thus far to live up to their promise, investigators reported at the annual meeting of the American Society of Clinical Oncology.

In an international multicenter phase III trial comparing the investigational antibody tremelimumab with standard single-agent chemotherapy, tremelimumab did not improve overall survival versus either temozolomide (Temodar) or dacarbazine (DTC), said Dr. Antoni Ribas, a medical oncologist at the University of California at Los Angeles Medical Center.

While tremelimumab didn't surpass standard chemotherapy, patients who received it had objective responses to the agent, many of which were sustained, Dr. Ribas said, concluding that it warrants further investigation for treatment of metastatic melanoma.

Tremelimumab is a fully humanized monoclonal antibody specific for cytotoxic T lymphocyte–associated antigen 4 (CTLA4). It blocks negative CTLA4 signaling, and has been shown in animal models and in vitro studies to induce significant activation of T cells at concentrations of 30 mcg/mL.

In a phase I/II clinical trial in 112 patients with measurable melanoma, tremelimumab produced objective responses in 11% of patients, and ongoing durable responses of 32-64 months in 8% of patients.

The phase III study was designed to test the hypothesis that tremelimumab could improve survival in patients with surgically incurable metastatic melanoma. It was funded by Pfizer Inc., developer of tremelimumab. The investigators chose a dose of 15 mg/kg on day 1 and then every 90 days.

The primary end point was overall survival with an improvement of at least 33% over the comparator, with secondary end points including best overall response, durable response, duration of tumor response, progression-free survival 6 months after randomization, and safety.

Stages IIIc and IV melanoma patients were randomized in a 1:1:1 ratio to either tremelimumab or to single-agent chemotherapy with either 1,000 mg/m^2 of dacarbazine intravenously on day 1 every 3 weeks, or 200 mg/m^2 of oral temozolomide on days 1-5 every 4 weeks.

The analysis was conducted on 324 patients who were assigned to receive tremelimumab and 319 assigned to the two chemotherapy regimens.

The trial was halted early after the second interim analysis in March 2008, when the data safety monitoring board determined that the study crossed the predetermined adjusted boundary for futility (*P* greater than .473), with a *P* value of .729.

A Kaplan-Meier estimate of overall survival among all patients in an intention-to-treat analysis showed median survival rates of 11.8 months for tremelimumab and 10.7 months for chemotherapy.

In an exploratory analysis of factors associated with overall survival, the authors found that "contrary to what had been anticipated, there is a trend toward better survival in the subset of patients with less advanced disease when treated with chemotherapy as opposed to tremelimumab," Dr. Ribas said.

In an intention-to-treat analysis of responses to therapy and 6-month progression-free survival, the complete response rate among 328 patients on tremelimumab was 1.5%, compared with 1.8% for 327 patients on chemotherapy. The partial response rates were 7.6% for patients who received the antibody and 8.3% for those on chemotherapy. The objective response rates (complete and partial responses combined) were 9.1% and 10.1%, respectively.

Six-month objective response rates (complete and partial responses combined) were 9.1% and 10.1%, respectively. Six-month progression-free survival was 18.6% for tremelimumab, vs. 14.1% for chemotherapy; this difference was not statistically significant.

Dr. Patrick Hwu, professor and chairman of medical oncology at the University of Texas M.D. Anderson Cancer Center, Houston, questioned whether overall survival was the best end point for the study, given that a subgroup of patients had a durable response to the anti-CTLA4 antibody.

Dr. Ribas has received honoraria, research funding, and served in an advisory role to Pfizer. Three of his coauthors are employees of the company. ■

High-Dose Interferon to Treat Melanoma Offers No Benefit

BY NEIL OSTERWEIL
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CHICAGO — The Sunbelt melanoma study did not meet its primary end point of showing a benefit of high-dose interferon in melanoma patients with a single positive sentinel lymph node, reported the principal investigator at the annual meeting of the American Society of Clinical Oncology.

In neither of two protocols comparing high-dose interferon to observation did the treatment arms show a significant benefit in either 5-year disease-free survival or overall survival among patients with a single positive node confirmed by histology or molecular studies.

Dr. Kelly McMasters, chief of the division of surgical oncology at the University of Louisville (Ky.), presented the data on behalf of his colleagues in the Sunbelt Melanoma Trial Group. The investigator-initiated trial, which involved 79 centers in the United States and Canada, registered 3,619 patients from the ages of 18 to 70 years with cutaneous melanomas with a thickness of at least 1 mm and no clinical evidence of regional nodal or distant metastases. Of these 1,781 were reported in the intention-to-treat analyses.

The patients were stratified according to Breslow thickness: 1.0-2.0 mm, 2-4 mm, and greater than 4 mm, and the presence or absence of ulceration.

The trial had two protocol arms and an unusually complex design. All patients underwent sentinel node biopsy, and those with a node that was confirmed positive on histology were eligible for protocol A, which involved completion lymph node dissection.

Patients with only one microscopically positive node were then randomized to either an observation arm (arm 1, with 112 patients) or to a treatment arm with high-dose interferon alfa-2b (Intron A) for 12 months (arm 2, 106 patients).

Patients with more than one positive lymph node or extracapsular extension were assigned to receive high-dose interferon for 12 months and were followed (arm 3, with 99 patients).

In protocol B, those patients who had histologically negative results after sentinel node biopsy subsequently had their sample tested with reverse transcriptase-polymerase chain reaction (RT-PCR) for molecular staging to detect the presence of occult melanoma cells. Those who were RT-PCR–positive were then randomized to either observation (arm 4, with 180 patients), completion lymph node dissection (arm 5, with 192 patients), or completion lymph node dissection plus interferon (arm 6, with 184 patients). Patients who were RT-PCR–negative were assigned to observation alone (arm 7, with 908 patients).

Dr. McMasters presented intention-to-treat analyses for each protocol. In protocol A, for patients with a single histologically positive sentinel node, the 5-year disease-free survival was 70.2% for arm 1 (the observation group) and 73.2% for arm 2 (the interferon group) (log-rank $P = .4589$). Five-year overall survival in these patients was 75.4% among patients on observation vs. 72.9% for those on interferon ($P = .9033$).

There were, however, statistically significant decreases in both disease-free and overall survival for patients in protocol A with more than one positive lymph node (arm 3), compared with arms 1 and 2. The 5-year disease-free survival for patients in arm 3 was 44.5% (*P* less than .0001 vs. arms 1 and 2), and overall survival was 52.9% ($P = .0004$).

In the disease-free survival analysis in protocol B, there were similarly no significant differences among patients randomized to observation, completion lymph node dissection, or completion lymph node dissection with interferon, with rates of 83.9%, 85.2%, and 83.7%, respectively.

For the same groups in the overall survival analysis, there were no significant differences, with rates of 85.5% for the observation arm, 85.3% for the node dissection alone arm, and 86.8% for the node dissection plus IFN arm. Similarly, there were no significant differences in either disease-free survival in protocol B between patients who were node-negative or node-positive on RT-PCR, or in overall survival, which indicated that PCR testing for melanoma cells was not prognostically significant in this study, Dr. McMasters remarked.

A comparison of all the patient treatment arms in the study showed that patients who were histologically node-negative (those in arms 4, 5, 6, and 7 combined) had a better overall survival rate than those with a single positive sentinel node (patients in arms 1 and 2 combined), who in turn did better than those who had more than one positive node or extracapsular extension (those in arm 3) (*P* less than .0001).

In protocol A, "our results did not support the use of high-dose interferon for patients with a single microscopically positive sentinel node," Dr. McMasters said.

In protocol B, the results do not support the use of completion lymph node dissection or interferon for node-negative patients, and indicate that RT-PCR staging of sentinel lymph nodes was not predictive of worse outcome.

Dr. McMasters noted that the study was underpowered to detect small differences in disease-free survival and overall survival, "but we also did not observe significant trends, and even large sample size will not make differences appear if they don't exist."

The study was supported by a grant from Schering Oncology Biotech. Dr. McMasters and several other investigators have been on the speakers bureau. ■