Phase III Trial Activity for Melanoma Is Robust

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — An unprecedented number of pivotal phase III trials of novel biologic therapies for melanoma are underway or about to start, according to speakers at the 11th World Congress on Cancers of the Skin.

"It's unbelievably busy in the field of melanoma," said Dr. Alexander M.M. Eggermont, professor and head of surgical oncology at Erasmus University Medical Center, Rotterdam, the Netherlands.

Among the biologic agents in phase III clinical trials for melanoma are cytotoxic T lymphocyte antigen 4 (CTLA4) blockers, apoptosis restorers, antiangiogenesis agents, and tyrosine kinase inhibitors. Numerous biologics are in earlier phase studies, including agents that interfere with melanoma's potent ability to repair chemotherapy-induced DNA damage. "The CTLA4 antibodies are the most exciting agents on the horizon," Dr. Eggermont commented at the congress, which was cosponsored by the Skin Cancer Foundation and Erasmus University.

Two such agents are in advanced development: ipilimumab, a Medarex/Bristol-Myers Squibb drug, and Pfizer's CP-675,206. Both are fully human monoclonal antibodies given by injection once every several months. CTLA4 blockade takes the brakes off T-cell proliferation, which results in an enhanced immunologic response to the tumor. These agents are in large phase III trials—some of them involving 1,000 advanced melanoma patients—as single-agent therapy, in combination with the alkylating agent dacarbazine (DTIC), as adjuvant therapy in patients with stage III or resected stage IV disease, or in conjunction with peptide vaccine therapy.

Until now, therapeutic melanoma vaccine development programs have been "remarkably unsuccessful," with no indication of any effect on survival, Dr. Eggermont said. The early evidence suggests CTLA4 blockers may change that. "We know we can induce immune responses. Many vaccine protocols have shown we can generate and induce T cell populations. The problem is we don't know how to maintain these T cell responses. Maintenance of the immune response is one of the critical barriers to successful development of vaccines. And here anti-CTLA4 is a crucial molecule."

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DR. EGGERMONT

The phase II trials of CTLA4 blockers in patients with stage IV melanoma have collectively shown confirmed tumor response rates of 10%-15%, with about one-quarter of responses being complete and the remainder being long-lasting partial responses. Another 30%-40% of treated patients have experienced prolonged disease stabilization. There have been documented responses of visceral and brain metastases. The price paid for this anticancer efficacy has come in the form of immune-related adverse events affecting primarily the skin, gastrointestinal, and endocrine systems.

An interesting attribute of the CTLA4 blockers is that more than 60% of confirmed responses occurred only after more than 12 weeks of therapy. These delayed responses initially showed static or even progressive disease before later developing into partial responses, and in some cases they later evolved into complete responses.

Dr. Céleste Lebbé, professor of dermatology and chief of dermato-oncology at Saint Louis Hospital (Paris) and the University of Paris VII, focused on the other agents in phase III: oblimersen (Genasense) and sorafenib (Nexavar).

Oblimersen is an antisense oligonucleotide that downregulates expression of the Bcl-2 protein. Bcl-2 overexpression inhibits apoptosis of cancer cells in response to chemotherapy or radiotherapy; Bcl-2 expression correlates negatively with treatment response and survival.

In a large phase III trial involving 771 patients with unresectable stage III or stage IV melanoma who were randomized to DTIC plus oblimersen or DTIC alone, the combination resulted in significantly better rates of overall response, complete response, durable response lasting more than 6 months, and progression-free sur-

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Safety of Solaraze for Actinic Keratosis Confirmed

BY BRUCE JANCIN
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AMSTERDAM — Diclofenac 3% gel was well tolerated and showed an excellent safety profile for treatment of multiple actinic keratoses in a postmarketing safety surveillance study.

The study, conducted in 140 primary care practices in the U.K., showed no severe treatment-related adverse events in 450 treated patients. The most common adverse events were mild to moderate dry skin, itching, and redness, each occurring in 16%-20% of patients, Dr. Ron Higson said at the 11th World Congress on Cancers of the Skin. Severe versions of these side effects occurred in fewer than 4% of patients.

Participants in this observational study applied diclofenac 3% gel (Solaraze) twice daily for 12 weeks to areas of actinic keratoses (AKs) in accord with the product labeling. The topical nonsteroidal anti-inflammatory drug is licensed for treatment of AKs in the United States, United Kingdom, and some other European countries. Patients were assessed during office visits at baseline and at weeks 6, 12, and 16.

There was also a secondary efficacy end point consisting of change over time in the longest AK axis from each patient's three largest AKs. The mean reduction in the size of AKs on the head, face, or neck was 2.8 mm at week 6 and 6.4 mm at the week 16 follow-up visit, Dr. Higson of Clitheroe (U.K.) Health Centre said at the congress.

Dr. Eggert Stockfleth, director of the skin cancer center at Charité University Hospital, Berlin, said diclofenac gel's two major advantages are its safety and the fact that it treats visible AK lesions as well as "field cancerization," the underlying dysplasia that gives rise to new AKs and eventually to skin cancers.

The congress was cosponsored by the Skin Cancer Foundation and Erasmus University, Rotterdam, the Netherlands. Shire Pharmaceuticals funded the study. ■

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vival (J. Clin. Oncol. 2006;24:4738-45).

Oblimersen failed to win regulatory approval in Europe or the United States based on this study because the trend for improved overall survival—the primary end point—didn't achieve significance, but overall survival was significantly better with combination therapy in the 508 patients with a normal baseline serum lactate dehydrogenase level, which was a prespecified stratification factor. Oblimersen's developer, Genta Inc., plans to conduct a repeat phase III trial, this time restricted to melanoma patients with normal lactate dehydrogenase levels, said Dr. Lebbé.

The Bayer drug Sorafenib is an antiangiogenesis agent by virtue of its inhibition of vascular endothelial growth factor 2, as well as an inhibitor of the mitogen-activated protein kinase signalling pathway with selectivity for the BRAF mutation present in 70% of melanoma patients. It quickly won regulatory approval in the United States and Europe for the treatment of renal cell carcinoma, and then for hepatocellular carcinoma, the most common malignancy worldwide. Results for melanoma have been mixed.

Clinical activity must be based on survival, and not response rates, which have not translated into improved survival.

DR. MIDDLETON

But Dr. Mark R. Middleton of Cancer UK and the University of Oxford (England) sounded a note of caution. "In melanoma we already have a wealth of therapeutic options. Untold numbers of drugs have been tested in our patients. Unfortunately, none of them work particularly well. The response rates are pretty dismal compared to those for most other solid tumors."

"The definition of promising clinical activity has to be based on survival rather than response rates … the higher response rates haven't translated into survival improvements," he said.

Dr. Middleton and Dr. Eggermont have received research funding from and are consultants to Schering-Plough. Dr. Eggermont is a consultant to Bayer, Boehringer Ingelheim, GlaxoSmithKline, Sanofi Pasteur, Onyx Pharmaceuticals, Genta Inc., and Synta Pharmaceuticals. Dr. Lebbé has received Novartis research funding. ■