Phase III Trial Activity for Melanoma Is Robust

Biologics being studied include CTLA4 blockers, apoptosis restorers, and antiangiogenesis agents.

BY BRUCE JANCIN
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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 these days," observed 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.

"I think 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.

Up 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. I predict it'll play an essential role across the board in vaccine development," he continued.

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.

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A particularly interesting attribute of the CTLA4 blockers is that more than 60% of confirmed responses have 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.

"This is totally new kinetics," Dr. Eggermont noted. "It's different from anything you've ever seen with chemotherapy."

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:** This antisense oligonucleotide 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 survival (J. Clin. Oncol. 2006;24:4738-45).

Oblimersen failed to win regulatory approval in Europe or the United States based upon 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 who had 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, Dr. Lebbé said.

► **Sorafenib:** This Bayer drug 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. (See article on p. 18.)

Although all of this extensive research activity involving new biologic agents for advanced melanoma may look promising, a cautionary note was sounded by Dr. Mark R. Middleton of Cancer UK and the University of Oxford (England), who has witnessed a relentless succession of therapeutic disappointments on the melanoma front during his career in medical oncology.

"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," Dr. Middleton observed.

Indeed, numerous combinations of chemotherapeutic agents or chemotherapy drugs and biologics—mainly interferons and interleukins—have been tested over the last 20 years. What these combinations have had in common was a weak therapeutic rationale and impressively high tumor response rates in mostly single-center phase II trials, which failed to translate into any overall survival advantage over DTIC alone in phase III studies.

"It's not that anybody's playing games with their phase-IIs, but naturally with combination regimens that you're trying for the first time you're going to enroll better, fitter patients and overestimate what you can get out of it, particularly if you're using historical controls," he explained.

"I think the definition of promising clinical activity has to be based on survival rather than response rates because we've clearly been caught out by the combination chemotherapy and biochemotherapy stories. It's very, very clear from that experience that the higher response rates haven't translated into survival improvements," Dr. Middleton added.

Dr. Middleton and Dr. Eggermont have received research funding from and are consultants to Schering-Plough.

In addition, Dr. Eggermont is a consultant to Bayer, Boehringer Ingelheim, GlaxoSmithKline, Sanofi Pasteur, Onyx Pharmaceuticals, Genta Inc., and Synta Pharmaceuticals. Dr. Lebbé has received research funding from Novartis. ■

Current Options in Stage IV Melanoma Deemed Unsatisfactory

BY BRUCE JANCIN
Denver Bureau

AMSTERDAM — Here's just how little progress has occurred in the systemic treatment of metastatic melanoma over the last 3 decades: Today the best therapeutic option for patients with advanced melanoma is to enroll them in a clinical trial of an investigational drug, Dr. Mark R. Middleton said at the 11th World Congress on Cancers of the Skin.

The standard treatment of advanced melanoma has for many years been single-agent dacarbazine (DTIC). None of the numerous multidrug combinations of chemotherapeutic agents or chemotherapeutic agents plus cytotoxic or biologic agents that have been tested have proved more effective than DTIC, only more toxic, he said.

Over the years, though, oncologists have come to realize that they have overestimated how good a drug DTIC is, said Dr. Middleton, a medical oncologist at Cancer Research UK and the University of Oxford (England).

Indeed, while decades-old studies suggested 20% of patients with advanced melanoma experience an objective tumor response to DTIC, more recent large multicenter studies indicate that the true figure is between 1 in 7 and 1 in 10, with no evidence DTIC offers any improvement over supportive care in terms of overall survival, he said at the congress, which was cosponsored by the Skin Cancer Foundation and Erasmus University.

This discouraging assessment isn't just one oncologist's view. Dr. Alexander M.M. Eggermont noted during his presentation that the Dutch Cancer Society recently issued an advisory that the No. 1 option in patients with advanced melanoma is to enter them into any new drug development trial, even a phase I trial.

"So phase I studies are the preferred option in stage IV melanoma patients, rather than giving them the usual stuff. I think that's a very important message because that's really what we need to move the field forward," added Dr. Eggermont, professor and head of surgical oncology at Erasmus University Medical Center, Rotterdam, the Netherlands, and president-elect of the Federation of European Cancer Societies. ■