Delayed Response Seen With New Melanoma Drugs

BY JANE SALODOF MACNEIL
Senior Editor

STOCKHOLM — Clinical studies of two experimental agents—tremelimumab and ipilimumab—have shown delayed and mixed responses among patients who gained control of refractory melanomas with these therapies.

Both agents come from a new class of monoclonal antibodies that seeks to promote immune response by blocking cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4). In three phase II trials presented at the European Society for Medical Oncology Congress, tremelimumab and ipilimumab ultimately achieved disease control rates of 14%-29% as second-line therapies.

Among patients classified as having progressive disease after ipilimumab treatment, however, were some people who subsequently improved. Likewise, among six patients with "mixed response" to tremelimumab were five patients who initially developed new lesions, but then had slow decreases in targeted lesions. All six were still alive at the time of the presentation.

Investigators suggested that the modified World Health Organization (WHO) criteria used to assess activity of cytotoxic agents may not capture the benefit in some patients classified with progressive disease. They cited four observed patterns of response, which were described in a poster by Dr. Kaan Harmankaya, of the department of dermatology at University of Vienna, and associates:

► Response in baseline lesions.

► Stable disease with a slow, steady decline in tumor volume.

► Response after increase in total tumor volume.

► Response in index and new lesions after the appearance of new lesions.

While delayed response is an issue for researchers, the clinical impact could be more important, according to a discussion of the tremelimumab and ipilimumab studies by Dr. Ulrich Keilholz of the Charité University in Berlin and the European Organisation for Research and Treatment of Cancer melanoma group.

"Nonclassical assessment does change the response rate, but it does not change the survival rate," Dr. Keilholz said, downplaying the importance of response, compared with overall survival in phase III trials.

Tremelimumab

Dr. John M. Kirkwood, director of the Melanoma Center at the University of Pittsburgh Cancer Institute, presented the tremelimumab data from an open-label phase II trial in 251 patients (nearly all with stage IV disease), of whom 242 were evaluable. The protocol called for a 15-mg/kg dose to be delivered intravenously on the first day of up to four 12-week cycles. Sixteen (7%) patients achieved partial responses and 36 (15%) had stable disease—a clinical benefit rate of 22%.

Dr. Kirkwood said all but 1 of the partial responses lasted at least 170 days, and 11 were ongoing. Median overall survival reached 10.1 months, he said; median progression-free survival reached 2.8 months, with 15.6% of patients progression-free 6 months after treatment. Factors correlating with survival were still being analyzed. The trial was sponsored by Pfizer Inc.

Ipilimumab

The first ipilimumab trial was a multinational, open-label study of 155 patients with advanced disease that had failed previous therapies. Patients received 10 mg/kg of ipilimumab every 3 weeks for four cycles, followed by maintenance therapy at the same dose every 12 weeks from week 12 to week 60.

Dr. Vanna Chiarion Sileni of the Instituto Oncologo Veneto in Padua, Italy, reported 9 patients had partial responses and 33 had stable disease by modified WHO criteria, adding up to a disease control rate of 27% (42/155). The median duration of stable disease was 4.1 months at a median follow-up of 5.7 months, she said; 19 patients were still stable at their last assessment.

Among those classified with progressive disease were patients with the four patterns of response. Small subgroups had a "slow steady decline" in tumor volume after an initial increase in target lesions or the appearance of new lesions, she said.

In the second ipilimumab trial, Dr. Celeste Lebbé of Saint-Louis Hospital in Paris reported on a multinational dose-finding study that randomized patients with unresectable relapsed stage III or IV melanoma to 10 mg/kg, 3 mg/kg, or 0.3 mg/kg of ipilimumab given once every 3 weeks for four cycles followed by maintenance treatment once every 12 weeks.

The 10-mg/kg dose produced the best overall response rate, a composite measure of complete and partial responses, at 11%, and a disease control rate of 29%. Nearly half, 48% of 73 patients given the highest dose were alive at 1 year. Their median survival was estimated at 11 months at a median follow-up of 10.4 months.

The four patterns of response were observed in this study as well, Dr. Lebbé reported, and about 35% of patients at the highest dose had a decline in total tumor volume. Patients at this dose also had the most toxicity, she said; about a quarter had grade III adverse events, including gastrointestinal side effects in 16%.

The ipilimumab studies were sponsored by Bristol-Myer Squibb and Medarex Inc, which are jointly developing the agent. Dr. Lebbé was the only investigator to disclose a conflict of interest, having served on two advisory boards for Bristol-Myer Squibb.

Dr. Kirkwood said phase III trials for both agents have been completed and are being analyzed, but applications for approval have not yet been filed. ■

Responses to Anti–CTLA-4 Agents

	Tremelimumab (n = 251)	Ipilimumab (n = 155)	Ipilimumab (n = 73)
Dose	15 mg/kg	10 mg/kg	10 mg/kg
Partial response	7%	6 %	11%
Stable disease	15%	21%	18%
Disease control rate	22%	27%	29%

Note: Data are from three phase II trials of experimental anti–CTLA-4 agents in patients with advanced refractory melanoma.
Sources: Dr. Kirkwood, Dr. Chiarion Sileni, and Dr. Lebbé

ELSEVIER GLOBAL MEDICAL NEWS

Negative Melanoma Results Have Some Asking, 'What's Next?'

BY JANE SALODOF MACNEIL
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STOCKHOLM — The failure of the largest randomized phase III trial ever conducted in stage IV melanoma has left investigators around the globe with a question for which they have no easy answer: What next?

Temozolomide did not improve upon the dismal survival rates achieved by standard therapy with dacarbazine (DTIC) in the disappointing multinational study presented at the European Society for Medical Oncology Congress. And some experimental treatments for advanced melanoma produced objective responses in less than 10% of patients reported upon by phase II investigators at the same meeting.

Moreover, DTIC may not be better than best supportive care—the two have never been tested against each other, according to Dr. Lorenz Jost, who painted a glum picture of melanoma research to date in his discussion of the temozolomide study.

"We don't have any proof that dacarbazine extends survival. Even worse, we don't have any proof that DTIC doesn't shorten survival," Dr. Jost of Kantonsspital Bruderholz in Switzerland told Congress attendees.

Except for the historical failure to compare DTIC to best supportive care, Dr. Jost found nothing wrong with the conduct of the European Organisation for Research and Treatment of Cancer (EORTC) 18032 trial comparing oral temozolomide with DTIC injection. At a median 18-month follow-up, median overall survival was little better than 9 months in both arms of the 859-patient study.

No chemotherapy combination has shown a significant advantage over DTIC, Dr. Jost said, citing a study comparing DTIC with vinblastine, bleomycin, and cisplatin (J. Clin. Oncol. 1984;2:164-8), nor have more aggressive regimens, such as one augmenting DTIC with cisplatin and carmustine (J. Clin. Oncol. 1999;17:2745-51).

Vaccines likewise have produced similar survival rates to DTIC (Ann. Onc. 2006;17:563-70), he continued, and a metaanalysis of 18 trials involving 2,621 patients randomized to biochemotherapies versus chemotherapy yielded an odds ratio of 0.99 for overall survival (J. Clin. Oncol. 2007;25:5426-34).

If DTIC cannot clear large tumors, Dr. Jost asked, can it be better used as an adjuvant therapy? No benefit has been seen with that approach, and boosting DTIC with sorafenib also produced no advantage in a study published earlier this year (J. Clin. Oncol. 2008;26:2178-85).

Maybe investigators should move on to a new class of drugs targeting cytotoxic T lymphocyte–associated antigen 4 (CTLA-4), he suggested, showing a list of about a dozen studies, among which only three trials reported patient responses (J. Trans. Med. 2008;6:22).

Despite all these red lights, Dr. Jost urged his audience not to despair. "Keep putting patients onto trials," he said.

But what trials? Even before Dr. Jost discussed the temozolomide results, an audience member suggested that perhaps it was time to stop doing phase III chemotherapy trials in melanoma.

Indeed, so many phase III trials have failed to improve survival rates in patients with late-stage melanoma that asking "What is your next phase III?" is to pose "a below-the-belt question," according to Dr. John M. Kirkwood, director of the Melanoma Center at the University of Pittsburgh Cancer Institute.

"We don't have an idea in the cooperative groups in the United States. Both the Southwest [Oncology Group] and the ECOG [Eastern Cooperative Oncology Group] are totally waiting for something in a blinding streak of brilliance," said Dr. Kirkwood, an ECOG investigator.

He reported on the investigational anti–CTLA-4 agent tremelimumab in a Pfizer Inc.–sponsored trial during the same session (see related story above). The bottom line seen in trials of tremelimumab and another experimental anti–CTLA-4 agent, ipilimumab, is that "objective response rates are very similar and there are people alive who wouldn't have been without these agents," he said in an interview. The main obstacle is anti–CTLA-4 therapy is "not efficient," with only a small number of people responding out of hundreds so far treated. The next step is to study proinflammatory cytokines and proteomics to identify factors predictive of response to these agents, Dr. Kirkwood said.

For Dr. Poulam M. Patel of the University of Nottingham (England), and investigator of the temozolomide trial, finding ways to identify molecular targets and subtype patients is likely to be the next direction taken by collaborative groups in melanoma. In his presentation, he also noted that no therapy has been proved more effective than DTIC in 2 decades. ■