Negative Melanoma Results Have Some Asking, ‘What’s Next?’

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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-mediated responses to the toxic 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% and partial responses of 10%-22% in advanced melanoma patients, respectively. 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 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 does not change 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. Sixty-six (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, and 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 Oncologico Veneto in Padua, Italy, reported 9 patients had partial responses and 11 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 3.7 months, she said; 19 patients were still stable at their last assessment.

Among those classified with progressive disease were 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 Lebè of Saint-Louis Hospital in Paris reported on a multinational dosing–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. Lebè 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., with which are jointly developing the agent. Dr. Lebè 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 undergoing analysis, but applications for approval have not yet been filed.

Delayed Response Seen With New Melanoma Drugs

Responses to Anti–CTLA-4 Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Disease control rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremelimumab</td>
<td>15 mg/kg</td>
<td>7%</td>
<td>1%</td>
<td>22%</td>
</tr>
<tr>
<td></td>
<td>10 mg/kg</td>
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<tr>
<td></td>
<td>10 mg/kg</td>
<td>15%</td>
<td>4%</td>
<td>22%</td>
</tr>
</tbody>
</table>

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. Lebè