

Clinical Perspectives™

Highlights from the Perspectives in Melanoma XII Conference

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REPORTS ON IMPORTANT ONGOING CLINICAL TRIALS

CTLA-4 directed antibodies

Steven O'Day, of The Angeles Clinic and Research Institute in Santa Monica, California, summarized the results from a multitude of trials performed to date examining CTLA-4-directed antibodies as treatment for advanced melanoma. The 2 anti-CTLA-4 antibodies currently in advanced stages of clinical development as melanoma treatment are tremelimumab (formerly CP-675,206 or ticilimumab) and ipilimumab (formerly MDX010). Both are fully humanized monoclonal antibodies, tremelimumab of the IgG2 subtype and ipilimumab of the IgG1 subtype. The plasma half-lives of tremelimumab and ipilimumab are 22 days and 12-14 days, respectively.

Phase 1/2 trials suggested that both tremelimumab and ipilimumab produced durable tumor responses (mostly partial responses) in at least a portion of melanoma patients and were associated with immune-related toxicities that correlated with clinical response. The data suggested an optimal dosing schedule for tremelimumab of 15 mg/kg every 12 weeks. The optimal schedule for ipilimumab is 10 mg/kg every 3 weeks during a 4-week induction period, followed by a 12-week rest period, and then 10 mg/kg once every 12 weeks for maintenance therapy. The dosing strategy for tremelimumab aims to reduce toxicity through infrequent administration, while the ipilimumab strategy is a more intense dose-dense approach, acknowledging some increase in toxicity, but recognizing that immune-related toxicities closely align with efficacy. Phase 1/2 trials have also begun to explore the possibility of combining anti-CTLA-4 antibodies with chemotherapy, interleukin-2, or vaccines.

Dr. O'Day briefly discussed the results from a recent randomized, open-label, phase 3 comparing tremelimumab with chemotherapy (either temozolomide [TMZ] or dacarbazine [DTIC], at the physician's discretion) in patients with unresectable stage IIIc or IV melanoma, no prior systemic treatment for advanced melanoma, no brain metastases, and serum LDH level <2× the upper limit of normal.¹ Data analysis showed single-agent tremelimumab therapy in patients with advanced melanoma did not provide a significant improvement in median overall survival (OS) compared with standard chemotherapy (11.8 vs 10.7 months; HR, 1.04; $P=0.729$). Objective tumor responses occurred in approximately 10% of patients in both treatment arms, but the duration of response appeared to be longer with tremelimumab. Dr. O'Day also discussed a recent open-label, phase 2 trial of tremelimumab treatment of patients with refractory or relapsed advanced melanoma. Updated data reported at the 2008 ESMO Congress indicated objective responses in 7% of tremelimumab-treated patients which were generally durable.² The median OS was 10.1 months, which compares favorably with the median OS of 6.2 months in other second-line phase 2 studies.³

With respect to phase 2 trials of ipilimumab, Dr. O'Day briefly touched on a number recently reported at ASCO 2008 and again in updated form at ESMO 2008. Study 022 was a dose-ranging trial that established 10 mg/kg induction and maintenance as the optimal regimens for patients with advanced melanoma.⁴ The 10 mg/kg dose was associated with an overall response rate (ORR) of 11.1%, a disease control rate (DCR: clinical response + partial response + stable disease) of 29.2% and a median OS of 11.0 months. Study 008 was an open-label, single-arm, phase 2 trial of ipilimumab in patients with advanced melanoma that progressed on 1 or more prior systemic therapies, and (in a report at 2008 ESMO) demonstrated a median OS of 6.2 months, an ORR of 5.8%, and a DCR of 27.2%.^{5,6} Study 007 was a randomized, double-blind, placebo-controlled, phase 2 trial comparing ipilimumab with or without prophylactic budesonide in patients with advanced melanoma.^{7,8} The aim was to see if budesonide treatment would prevent ipilimumab-related gastrointestinal AEs. The final

results indicated no difference in gastrointestinal or other AEs in patients who did or did not receive budesonide with ipilimumab. The ORR in the 2 groups ranged from 12.0% to 15.8%, the DCR from 31.0% to 35.1%, and the median OS from 15.1 to 17.2 months.

Across all phase 2 ipilimumab trials, investigators noted nontraditional tumor responses currently classified as PD (progressive disease) by RECIST criteria in approximately 10% of ipilimumab-treated patients, most notably objective responses that occurred over time after initial stable disease, initial increase in total tumor volume, or after appearance of new lesions. These nontraditional responses may be related to the mechanism of action of anti-CTLA-4 antibodies, which presumably require some passage of time for maximal response.

In addition to these phase 2 trials, Dr. O'Day also mentioned a phase 3 comparing ipilimumab plus DTIC with DTIC alone in patients with advanced melanoma that has recently been completed, but for which results were not available at the time of the *Perspectives in Melanoma* conference. The primary endpoint for the study is OS. In addition, an ongoing randomized controlled study (n=950) is comparing ipilimumab (10 mg/kg) with placebo as adjuvant therapy in stage III patients at high-risk for disease recurrence following resection. The primary endpoints are OS and recurrence-free survival.

Dr. O'Day noted the findings to date appear to be generally similar for tremelimumab and ipilimumab. Classic tumor responses (per RECIST or modified WHO criteria) occur in 5% to 15% of patients, and nearly all are durable. Another 10% to 20% of patients exhibit stable disease as best response, for a DCR of around 30%. The majority of these are also durable. Late/nonclassical responses are observed in another 10% of patients after initial progression, and again these are generally durable. Median OS appears to be in the range of 10 to 15 months, which Dr. Day noted is encouraging. However, currently available results from anti-CTLA-4 antibody studies suggest there may be a long-term plateau of about 30% to 40% patient survival. Longer follow-up will be required to more fully test this hypothesis. Both tremelimumab and ipilimumab are associated with grade 3/4 immune-related AEs in 20% to 30% of patients, and appearance of these AEs seems to correlate with or be a predictor of disease control and OS.

References

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Elesclomol

Steven O'Day presented data from a randomized, double-blind, active-controlled, phase 2 trial comparing elesclomol (formerly STA-4783) plus paclitaxel with paclitaxel alone in patients with stage IV melanoma. Similar data were presented by Dr. O'Day at the ESMO congress about 1 month earlier. The metabolic requirements of rapidly proliferating melanoma cells leads to a state of oxidative stress, associated with elevated levels of reactive oxygen species (ROS). ROS activates signaling pathways leading to apoptosis, and elesclomol rapidly induces the generation of ROS in melanoma cells, thereby presumably overwhelming any antiapoptotic mechanisms in these cells, and pushing them to cell death via apoptosis. Because normal cells are under less oxidative stress than melanoma cells, the apoptotic effects of elesclomol are expected to be selective for melanoma. Traditional chemotherapy agents generate ROS as a secondary event, hence the rationale for combining elesclomol and chemotherapy to produce additive/synergistic effects on ROS level.

In the phase 2 study described by Dr. O'Day, 81 patients with stage IV melanoma, 0-1 prior chemotherapy for metastatic disease, Eastern Cooperative Oncology Group (ECOG) PS 0-2, and no brain metastases were randomized in 2:1 ratio to receive 3 weekly treatments per 4-week cycle until progression of elesclomol (213 mg/m²) plus paclitaxel (80 mg/m²) or paclitaxel alone (80 mg/m²). The primary endpoint was PFS, and crossover was allowed for the paclitaxel-alone arm after progressive disease. The results were promising in that elesclomol plus paclitaxel versus paclitaxel alone was associated with significantly longer median PFS (3.7 vs 1.8 months; HR, 0.58; $P=.035$) and a trend for higher ORR (15.1% vs 3.6%; $P=.15$). Improvement in median PFS with the combination regimen was observed regardless of M-grade status (3.5 vs 3.7 months for low- and high M-grade), but appeared to be greater in patients with no versus 1 prior chemotherapy regimen (7.1 vs 2.8 months). Median PFS with paclitaxel alone was 1.8 months regardless of M-grade status or prior chemotherapy status.

Although median OS did not differ for the elesclomol plus paclitaxel versus paclitaxel alone groups in the intent-to-treat sample (11.9 vs 7.8 months; HR, 0.88; 95% CI, 0.53-1.48; $P=.63$), this may have been due to the confounding effects of crossover. In addition, the study was not powered for survival endpoint. Analysis of OS by treatment and crossover showed higher median OS for patients in the elesclomol plus paclitaxel (11.9 months) group and those in the paclitaxel-alone group who crossed over to combination therapy (14.3 months) than in those in the paclitaxel-alone group who did not cross over (5.6 months). Elesclomol plus paclitaxel was associated with acceptable tolerability/safety, and the combination is being further explored in the phase 3 SYMMETRY trial. The SYMMETRY trial will enroll 630 or more patients with stage IV melanoma and no prior chemotherapy, and randomize them in a 1:1 ratio to receive elesclomol plus paclitaxel or paclitaxel alone, without allowance for crossover. PFS will be the primary endpoint, and OS is a secondary endpoint.

Nab-paclitaxel (ABI-007) in metastatic melanoma

Nanoparticle albumin-bound paclitaxel, or *nab*-paclitaxel, is paclitaxel that has been bound to albumin. Traditional paclitaxel contains the solvent Cremophor (polyethoxylated castor oil), which is required to dissolve the drug before it can be administered intravenously (IV). *Nab*-paclitaxel does not contain solvents and has a number of potential benefits compared with standard paclitaxel, including no need for premedication to prevent solvent-related hypersensitivity, shorter infusion time (30 minutes), and possibly improved efficacy. *Nab*-paclitaxel is currently approved by the FDA for the second-line treatment of breast cancer. **Axel Hauschild**, of the University of Kiel, Germany, discussed the results from 3 recent studies evaluating *nab*-paclitaxel in patients with advanced melanoma.

The first study Dr. Hauschild discussed was an open-label, phase 2 trial comparing *nab*-paclitaxel in previously-treated (n=37) or chemotherapy-naïve patients (n=37) with advanced melanoma, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1, and no brain metastases. *Nab*-paclitaxel was administered via 30-minute IV infusion every 3 weeks out of 4 (1 cycle) until progression or unacceptable toxicity, at 100 mg/m² for previously-treated patients and 150 mg/m² for chemotherapy-naïve patients. One patient in the previously-treated cohort (3%) and 8 in the chemotherapy-naïve cohort (22%) had a confirmed partial response (PR). There were no clinical responses reported. Fourteen in the previously-treated group (38%) and 18 in the chemotherapy-naïve group (49%) had stable disease ≥16 weeks or PR. Median PFS was 3.5 months in the previously-treated cohort and 4.6 months in the chemotherapy-naïve cohort, and median overall survival (OS) was 12.1 months and 9.6 months, respectively. Median PFS and OS were better in both groups for patients with normal serum LDH versus elevated serum LDH. Tolerability results were unremarkable. Toxicity was mainly attributed to hematologic side effects, rarely reaching grade 4. Incidence of grade 3/4 toxicities was slightly higher in the chemotherapy-naïve cohort.

The second study reviewed by Dr. Hauschild was a phase 2 trial (N057E) evaluating the combination of *nab*-paclitaxel (100 mg/m²) and carboplatin (AUC2) in patients with advanced melanoma, ECOG PS 0-2, and no prior chemotherapy. Both treatments were administered on days 1, 8, and 15 of a 28-day cycle. Preliminary results of this study were presented at the 2008 ASCO meeting.¹ There were 10 confirmed PRs (26%) in the 39 clinically evaluable patients. The median PFS and OS were 4.3 and 10.0 months, respectively. The most common grade 3/4 toxicities were neutropenia (31%), thrombocytopenia (5%), and neurosensory AEs (5%). Hence, the combination of *nab*-paclitaxel and carboplatin appears to be well tolerated and shows promising clinical activity in chemotherapy-naïve patients with advanced melanoma.

Finally, Dr. Hauschild discussed initial findings from an ongoing phase 1/2 study designed to evaluate the feasibility and efficacy of triple therapy with *nab*-paclitaxel, oblimersen (OBL), and TMZ in patients with advanced melanoma, ECOG PS 0-2, normal serum LDH, and no prior chemotherapy. In addition, tumor biopsies were obtained at pretreatment and day 29 to evaluate BCL-2, BAK, BCL-X, and caspase-3 levels. Results of this study were presented at the 2008 ASCO meeting.² Of the 14 clinically evaluable patients (cohort 1), 1 (7%) had a confirmed clinical response after 6 cycles, 5 (36%) had PRs confirmed after 1 cycle, and 3 (21%) had stable disease lasting at least 3 cycles (24 weeks). Alopecia, leukopenia, and neutropenia were the most frequently reported AEs, and there were few grade 3/4 toxicities. Responding patients showed homogenous tumor staining for BCL2, BAK, and BCLX after treatment, while nonresponding patients demonstrated no change in staining treatment. Caspase-3 levels were unchanged in all patients. The authors of the ASCO presentation concluded that initial results suggest that first-line treatment with this triple combination is associated with minimal and no dose-limiting toxicity, and evidence of clinical activity, in this patient population.²

Summarizing the findings from the 3 studies, Dr. Hauschild concluded that *nab*-paclitaxel showed significant antitumor activity in advanced melanoma either as a single agent or in combinations in this non-taxane setting. Toxicities were tolerable and manageable. He reported a large, prospective, randomized phase 3 trial of chemotherapy with *nab*-paclitaxel versus DTIC for advanced melanoma is in the final planning stage.

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Bevacizumab

Paul Lorigan, of Christie Hospital NHS Trust in Manchester, United Kingdom, provided a brief update of the ongoing Adjuvant aVASTin Trial in high-risk Melanoma (AVAST-M). AVAST-M is a randomized, multicenter, phase 3 trial evaluating BEV versus observation as adjuvant therapy for postresection stage IIB-III melanoma patients at high-risk for disease recurrence.

A total of 1,320 patients will be randomized no sooner than 4 weeks and no later than 12 weeks after completion of latest melanoma surgery (primary resection, wide local excision, removal of in-transit metastases, or lymphadenectomy). Patients are stratified by Breslow thickness, ulceration, type of nodal involvement, number of positive nodes, and gender. The primary endpoint is overall survival; secondary endpoints include distant metastasis free interval, disease-free interval, quality of life, and safety/tolerability. In addition, biomarkers for angiogenesis are being measured in tissue and peripheral blood to identify potential prognostic/predictive factors. BEV is administered as 7.5 mg/kg IV every 3 weeks for 51 weeks, for a maximum of 17 infusions over 1 year or until disease progression. Intended follow-up is 10 years or until death. Exclusion criteria are typically for studies of antiangiogenic treatments.

By the October 2008 *Perspectives in Melanoma* conference, 184 patients had been recruited. There are 31 United Kingdom sites currently open to recruitment, and approximately 10 more are at various stages of preparation. The estimated date of recruitment of all 1,320 patients is late 2011. Dr. Lorigan presented the initial safety/toxicity data for the first 184 patients enrolled in the study, 63 in the BEV arm and 65 in the observation arm. The mean duration of treatment for those in the BEV arm is 3.1 months. To date, there have been 8 patient withdrawals from the BEV arm, 4 for distant recurrence, 2 for toxicity, 1 for local recurrence, and 1 for withdrawn consent. There have been 3 serious AEs (optic nephritis, infected seroma, abdominal pain), 1 thought to be associated with BEV treatment, and no treatment-related deaths. There were 2 SAEs in the observation arm—skin infection and spinal cord compression due to disease progression. A formal review by the Data Safety Monitoring Committee will be conducted after 300 patients have been recruited, and this is scheduled for March 2009.

Overall, Dr. Lorigan concluded, a 12-month safety review of AVAST-M suggests adjuvant BEV is very well tolerated. There is excitement in the field about AVAST-M, he stated, and subsequent findings concerning updated safety/tolerability, efficacy, and evaluations of potential prognostic/predictive markers are eagerly anticipated.

Thymalfasin

Michele Maio, of the University Hospital of Siena in Siena, Italy, described promising results from a phase 2 trial of thymalfasin plus additional agents in patients with advanced melanoma. Thymalfasin (thymosin- α 1) is a 28-amino acid peptide with immunomodulatory properties that probably relate to its mechanism of activity in cancers such as melanoma. More specifically, thymalfasin has been reported to promote T-cell production, increase levels of interleukin-2 and interferon (IFN)- γ , increase expression of tumor antigens, and decrease apoptosis, among other actions. In the study reviewed by Dr. Maio, patients with previously untreated stage IV melanoma were randomized to receive dacarbazine (DTIC) + IFN- α (n=97), DTIC + thymalfasin 3.2 mg (n=99), DTIC + IFN- α + thymalfasin 1.6 mg (n=97), DTIC + IFN- α + thymalfasin 3.2 mg (n=97), or DTIC + IFN- α + thymalfasin 6.4 mg (n=98). DTIC (800 mg/m²) was administered on day 1 of an 18-day cycle, IFN- α (3MIU) on days 11 and 18, and thymalfasin (1.6, 3.6 or 6.4 mg, once daily) on days 8-11 and days 16-18. The objective of the study was to select a dose/schedule of thymalfasin-based therapy for further investigation. The primary endpoint was tumor response as assessed by RECIST.

The median follow-up for the various treatment groups ranged from 30.3 to 33.9 months for all groups, except for the group receiving thymalfasin 6.4 mg (median, 19.6 months). The best response appeared to occur with DTIC + thymalfasin 3.2 mg, and secondarily with DTIC + IFN- α + thymalfasin 3.2 mg. For example, the overall response rate (ORR) with DTIC + thymalfasin 3.2 mg was 12.1% (10.1% partial response and 2.0% clinical response), compared with 4.1% (all partial responses) with DTIC + IFN- α . When

patients with elevated serum LDH ($>1.0\times$ the upper limit of normal [ULN]) were excluded, the corresponding ORR results were 13.3% and 3.2%, respectively. Similarly the proportion of patients with overall survival (OS) at 12 months and PFS at 6 months in the DTIC + IFN- α + thymalfasin 3.2 mg group was 38.8% and 15.9%, respectively, and 60.7% and 22.8% when the analysis was restricted to patients with serum LDH $<1.0\times$ ULN. By comparison, the percentages with DTIC + IFN- α were 33.2% for OS and 9.1% for PFS, and when restricted to patients with serum LDH $<1.0\times$ ULN, 46.3% and 8.2%, respectively. No additional toxicity was observed with the additional of thymalfasin to DTIC or DTIC + IFN- α .

Dr. Maio concluded that the addition of thymalfasin to standard DTIC treatment for advanced melanoma resulted in a reduction in risk of mortality and disease progression. The risks were further reduced in patients with normal serum LDH levels. Moreover, the results here support conduction of a phase 3 trial and, in fact, such a trial is under development to compare DTIC + thymalfasin with DTIC + placebo in patients with stage IV melanoma, using median OS as the primary endpoint.

Oblimersen

Oblimersen sodium (OBL) is an antisense oligonucleotide targeting Bcl-2 mRNA. Bcl-2 is an antiapoptotic protein that has been linked with chemotherapy resistance in melanoma. **Claus Garbe**, of the Eberhard-Karls-University in Tuebingen, Germany, discussed the findings from a recent study comparing dacarbazine (DTIC) with or without oblimersen in patients with advanced melanoma, and described the design of the ongoing AGENDA trial, which is also comparing DTIC with or without OBL in advanced melanoma patients. Both are randomized phase 3 trials.

Results from the first trial were published in 2006 in the *Journal of Clinical Oncology*.¹ In the study, 771 patients with advanced melanoma and no prior chemotherapy were randomly assigned to treatment with DTIC alone (1,000 mg/m²) or DTIC preceded by 5-day treatment with OBL (7 mg/kg/d) every 3 weeks for up to 8 cycles. Patients were stratified for baseline LDH, metastatic disease site, and ECOG PS. The primary endpoint was overall survival (OS). The efficacy summary at 24 months minimum follow-up showed a trend for longer median OS with OBL plus DTIC versus DTIC alone (9.0 vs 7.8 months; HR, 0.87; $P=.077$), and significantly longer median PFS with the combination regimen (2.6 vs 1.6 months; HR, 0.75; $P<.001$). In addition, OBL plus DTIC versus DTIC alone was associated with significantly greater overall response (13.5% vs 7.5%; $P=.007$), complete response (2.8% vs 0.8%; $P=.031$), and durable response (7.3% vs 3.6%; $P=.03$). Furthermore, Dr. Garbe noted, median OS was significantly longer with the combination regimen for patients with normal LDH at baseline, (11.4 vs 9.7 months; HR, 0.79; $P=.02$) and the best results were obtained in the subgroup of patients ($n=274$) with serum LDH level $0.8\times$ the upper limit of normal (ULN) (12.3 vs 9.9 months; HR, 0.64; $P=.0009$).

Dr. Garbe then turned his attention to AGENDA, the second randomized phase 3 trial of OBL in advanced melanoma. This study has been designed to compare DTIC alone ($n=150$) with DTIC plus OBL ($n=150$) in previously untreated patients with advanced melanoma and LDH level $\leq 0.8\times$ ULN. The dosing regimens are the same as in the previous phase 3 trial. OS and PFS are dual primary endpoints. The primary objective of the AGENDA trial is to confirm the OS result in the subpopulation of patients with LDH level $\leq 0.8\times$ ULN. Multiple sites in 12 countries are participating in the study. At the time of the *Perspectives in Melanoma* conference, 150 patients had been enrolled, and initial safety/tolerability data were available. Complete enrollment was expected by first quarter 2009. Baseline demographic and disease characteristics were generally similar in the AGENDA population as in the prior phase 3 trial. Percentage of serious adverse events (AEs) also appeared similar for the 2 trials (14% vs 18% in AGENDA). In general, the safety/tolerability profile of OBL is predictable and manageable, Dr. Garbe said.

Reference

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