FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Oncologic Drugs Advisory Committee Meeting
May 3, 2004

Questions to the Committee

NDA 21-649 Genasense (Oblimersen sodium), Genta, Inc.

Indication Genasense in combination with dacarbazine is indicated for the treatment of patients with advanced melanoma who have not received prior chemotherapy.

Genta has submitted a single, international, multi-center, unblinded, active control, randomized, phase 3 study (GM301) of Genasense plus dacarbazine (DTIC) versus DTIC alone every three weeks as first-line chemotherapy for metastatic melanoma, along with a small, supportive, single arm, phase 1/2 study with various doses and schedules of Genasense plus DTIC. In the phase 3 study, Genasense was given as a continuous intravenous (IV) infusion over 5 days, requiring central venous access and an ambulatory pump. DTIC 1000 mg/m2 IV was given over 60 minutes once every three week cycle in each study arm.

The primary endpoint of the trial was survival. Secondary endpoints were progression-free survival (PFS), response rate (RR), response duration, performance status, tumor-related symptoms, and safety.

The results from the phase 3 study submitted for efficacy are presented in the table below.

GM301 results

Endpoint	Genasense + DTIC (N=386)	DTIC alone (N=385)	Hazard Ratio	p-value
Survival	274 days	238 days	0.89	0.18
PFS*	61 days	48 days	0.75	0.006
Response Rate by Investigators	11.7%	6.8%		0.019
Response Rated Confirmed by Independent Review Committee	6.7%	3.6%		0.056

* PFS by censoring on the date of the last complete evaluation.
Reviewer's Table

Genta proposes that these study results be considered evidence of effectiveness. FDA has a number of important concerns. First, the study clearly did not show the improvement in survival that was the stated endpoint. Second, the PFS endpoint although nominally improved by Genasense + DTIC has two important problems. First the effect is very small, well under one month. Second in an open study, there is concern that critical decisions such as when to obtain radiological films, could be biased. In this study lesion assessments were done earlier in the DTIC alone group ($p < 0.001$). This could lead to earlier documentation of progression. Thus, it is a concern whether the observed difference is real. Except possibly for response rate, no other secondary endpoints demonstrated an advantage of Genasense + DTIC over DTIC alone. Furthermore, it is not clear that the small difference in PFS observed is clinically meaningful, especially in view of the observed Genasense toxicity.

A recent ODAC consideration of temozolomide (TMZ) for the treatment of metastatic melanoma (NDA 21-051) appears pertinent. As in the present application only one phase 3 trial was submitted in support of the indication. The median survival on the DTIC arm was 6.4 months versus 7.7 months for TMZ, a difference in median survival of 1.3 months. Although 80% of the events had occurred by the time of the analysis, the difference was not statistically significant ($p=0.2$). A post-hoc analysis suggested an improvement in survival at 6 months (61% for temozolomide versus 51% for DTIC, $p=0.063$), but the Committee did not consider this post-hoc finding to be convincing. Additional secondary endpoints reviewed were response rate and PFS. The Agency's analysis showed that median PFS was 1.74 months for TMZ versus 1.38 months for DTIC, a difference of less than a month, but statistically significant ($p=0.002$). Additional post-hoc exploratory analyses included possible prolongation in PFS for some patients in the third quartile of the survival curve before the curves came together again at 14 months. No symptomatic benefit was identified in association with this difference. The Agency compared response rates for the 2 arms; the ORR for TMZ was 12.2% (2.6% CR), versus 9.4% for DTIC (2.7% CR).

During the Advisory Committee meeting, members considered two questions with regard to the Temozolomide application. The questions were:

1) Do the results of this study, particularly the objective tumor response rates and response durations for the temozolomide versus dacarbazine, and the effect on progression-free survival, even in the absence of any effect on survival provide substantial evidence of effectiveness?
2) Does the Committee recommend approval of temozolomide for the treatment of advanced metastatic melanoma?

The vote on the first question was 10 No and one abstention. On the second question the vote was 10 No and 1 Yes.

TMZ, thus, was not recommended for approval because the trial did not show superiority in survival to DTIC alone. The small but statistically significant difference in PFS ($p = 0.002$) and slightly higher response rate, in the absence of any evidence of survival or symptomatic benefit, were not thought to represent a meaningful benefit.

In the recent case for Genasense, the GM301 study failed to demonstrate an effect on survival, the primary trial endpoint. No effects were seen on performance status or tumor-related symptoms, and there was greater toxicity on the Genasense arm. The PFS improvement was significant but the difference was very small and there may have been a difference in progression ascertainment that favored Genasense. Similarly, a small increase in response rate increment attributed to Genasense is somewhat uncertain because a central reading (potentially, particularly important in an open study) showed no significant difference. We would like the panel to comment on whether improvement in PFS and RR of this magnitude, apart from not being clearly identified planned study endpoints and any reservations about the validity of the findings, would represent a benefit both on the persuasiveness of the PFS and RR findings and one that would outweigh the increase in toxicity seen with the combination. No evidence from this study suggests that changes of this size represent or are likely to predict clinical benefit, but that is an issue that bears discussion.

Questions:

1. Given the concerns noted above, does the committee believe that the small observed differences in the response rates (< 5%) and in PFS (difference in median days between arms -13 days, p = 0.006) represent real effects of Genasense, when added to DTIC?

2. Do the results of this study, in particular the small difference in RR (<5%) and / or PFS for the combination of Genasense + DTIC versus DTIC alone, in the absence of a survival improvement, provide substantial evidence of effectiveness that outweighs the increased toxicity of administering the Genasense for the treatment of patients with metastatic melanoma who have not received prior chemotherapy?

3. For regular approval of a drug for metastatic melanoma, the FDA has considered an improvement in survival and/or disease symptoms to constitute clinical benefit. However, in the December ODAC discussion, considerable interest was expressed in PFS as an endpoint in some settings, particularly where crossover to other treatment could obscure a potential survival benefit. In the metastatic melanoma setting, do you believe that a PFS benefit of some magnitude represents clinical benefit that could support regular drug approval, even in the absence of an effect on survival?

4. If yes, please discuss what magnitude of improvement in this endpoint would be required to demonstrate clinical benefit and whether this would depend on the toxicity of the treatment?