Oncologic Drugs Advisory Committee
DRAFT MINUTES
December 17-18, 2002

The 73rd meeting of the Oncologic Drugs Advisory Committee was held in the Versailles Ballroom at the Holiday Inn at 8120 Wisconsin Avenue, Bethesda, Maryland. Approximately 300 people were in attendance on December 17 and approximately 125 on December 18. The meeting was chaired by Donna Przepiorka, MD, PhD.

Open Public Hearing

Thom Jones – Pittsburgh, Pennsylvania
Erica Hertz – The Wellness Community
Patricia and Joseph Bashaw – Brookfield, Wisconsin
Kent Halbach – White Bear Lake, Minnesota
Pat Haut – Auburn, Michigan
Frank Burroughs – The Abigail Alliance for Better Access to Developmental Drugs
Tom McDermitt – Glenside, Pennsylvania
Leonard Greer – Rye, New York
Alida Diab – Princeton, New Jersey

BL STN 125011/0, Bexxar®, Tositumomab (Anti-B1) and Iodine^{131}-Tositumomab, Corixa Corporation

- indicated for the treatment of patients with relapsed or refractory low-grade, follicular or transformed low-grade, B-cell non-Hodgkin's lymphoma (NHL) including patients with rituximab refractory follicular non-Hodgkin's lymphoma

Introduction to Tositumomab Therapeutic Regimen	Terrye G. Zaremba, Ph.D. BLA Committee Chairperson CBER, FDA
Sponsor Presentation	**Corixa Corporation**
Disease Outcome and Therapy for Low-Grade and Transformed NHL	Richard Fisher, M.D. University of Rochester
Efficacy and Safety Overview: Basis for Approval	Cindy Jacobs, Ph.D., M.D. Senior Vice-President, Clinical Research
Risk/Benefit Assessment	James Armitage, M.D. University of Nebraska
FDA Presentation	Center for Biologics Evaluation and Research Stephen Litwin, M.D. Medical Reviewer, FDA

The Committee Discussion was led by ODAC Consultants James Krook, M.D. and James Bridges, M.D.

Questions to the Committee

STN 125011 Tositumomab Therapeutic Regimen, Corixa Corporation

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The response rates and durations to the TTR observed in 5 studies of the treatment of patients with chemotherapy-refractory and Rituximab-refractory, low grade and follicular NHL without or without transformation are summarized in table 1.

Study Number	Design	Median # of Prior Chemo Regimens (range)	Overall Response Rate (95% CI)	Complete Response Rate (CR +CCR)	Median Duration of Response (yrs)	Duration of Response 25^{th} & 75^{th} quartiles (yrs)
RIT-II-004 (N=61)	**Chemo-refractory**	**4 (2-13)**	**46% (33%, 59%)**	**20%**	**1.0**	**0.3, 3.9**
CP-97-012 (N = 43)	**Rituximab -refractory**	**4 (1–11)**	**63% (47%, 77%)**	**30%**	**1.3**	**0.8; NR**
RIT-I-000 (N=59)	**MTD**	**3 (1-11)**	**48% (34%, 61%)**	**27%**	**1.0**	**0.6; 3,8**
RIT-II-001 (N = 47)	**Dosimetry**	**4 (1–8)**	**49% (34%, 64%)**	**26%**	**1.2**	**0.4; 4.9**
RIT-II-002 (N = 42)	**Hot vs. cold**	**2 (1–4)**	**55% (39%, 70%)**	**33%**	**NR**	**0.4; NR**

The 5 studies conducted and monitored by the sponsor to assess clinical activity enrolled 229 patients who received the dose and schedule for which approval is being sought (specifically, a single dosimetric infusion followed 7-14 days later by a therapeutic infusion of 131-I-tositumomab at 75cGy total body dose, with adjustments for obesity or mild thrombocytopenia).

The toxicities of the TTR are related both to the radioisotope (131-Iodine) component and to the murine monoclonal antibody. The toxicities that are primarily due to the radioisotope include neutropenia, thrombocytopenia, and anemia in 64%, 54%, and 19% of the patients respectively with a median time to nadir of 4 to 6 weeks and duration of nadir (NCI CTC grade 3-4) of approximately 4-6 weeks. Infections were reported in 43% of patients and hemorrhagic events in 12%; the majority of these clinical sequelae of myelosuppresion were not serious. In addition, secondary leukemias, solid tumors and myelodysplasia were observed. Subacute gastrointestinal toxicity from radiation can occur. Finally, hypothyroidism has been observed with a cumulative rate of 30% at 5 years and 45% at 7 years across the clinical studies.

In addition, there are toxicities that are primarily due to the tositumomab (mouse antibody) component. These include

- infusion reactions, which occur in approximately 50% of patients and can be severe
- gastrointestinal toxicity due to binding in lymphocytes in the GI tract which is acute and peri-infusional (cold antibody- mediated)- described in
- a decrease in circulating CD20+ cells,and

- the development of an immune response to the murine antibody, which reaches a cumulative incidence of 20% at approximately one year (as lymphocyte recovery occurs).

  There may be an interaction between the lymphopenia due to tositumomab and the neutropenia due to 131-Iodine to result in an increased risk of infection (48% cumulative incidence of infection).

Rituximab-refractory, follicular NHL

The Zevalin therapeutic regimen was evaluated by the ODAC on September 11, 2001. The Committee recommended standard approval for Zevalin for the treatment of patients with Rituxan-refractory, follicular NHL, based upon an ORR of 59% and median duration of response of 6.8 months in a single arm trial, supported by preliminary survival data from a randomized, controlled trial conducted in chemotherapy-refractory, Rituximab-naïve patients. The supportive study in Rituximab-naïve patients showed no evidence of impairment of survival in 143 patients equally allocated to the Zevalin therapeutic regimen vs. Rituximab at the approved dose and schedule.

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At the time of the original submission of BLA 125011, several of the trials listed above were ongoing. In responding to FDA's requests for additional safety and efficacy information, the final study report for CP97-012 was submitted September 7, 2001 and an amended final study report for CP97-012 was submitted in July 11, 2002. This is the only study that assesses the activity of the tositumomab therapeutic regimen in patients whose disease is refractory to, or only transiently responsive to, Rituximab. The sponsor has requested an indication for the treatment of patients with follicular lymphoma, a subset of the patients enrolled. In this subpopulation the ORR was 63% and the median duration of response 2.1 years. TTR activity was similar for the overall study population (n=43), which included patients with low-grade, non-follicular (IWF A) and low-grade-transformed NHL (ORR 63%, median duration of response 1.3 years).

Questions to the Committee

1. **Do the results (ORR 63%, median response duration 2.1 years) in 30 patients enrolled in this Phase 2 study (CP97-012), supported by the results observed in the other patients enrolled in this study and the activity in studies conducted in Rituxan-naïve patients with chemotherapy-refractory disease, constitute substantial evidence of clinical benefit?**

   YES – 10 ***N - 3***

   The Committee felt that this implicitly-controlled trial was small, but there did appear to be evidence of clinical benefit and a response of long duration. Concerns were expressed about the quality of the data, including the number of protocol violations, and the observed myelodysplasia as an adverse event.

Chemotherapy-refractory low grade and follicular NHL, with or without transformation

2. **Are the overall response rates and durations of responses observed across the 5 clinical trials conducted by the sponsor, in light of the toxicity profile observed, likely to predict clinical benefit in patients with chemotherapy-refractory, low grade and follicular NHL, with or without transformation?**

YES – 13 ***N - 0***

The Committee felt that, in these heavily pre-treated patients, this product produced a reasonable number of responses of good duration, and appeared as least as good as another line of cytotoxic treatment. Concerns about the hematologic toxicities and long term risks should be addressed in the informed consent forms, and make this treatment inappropriate for first-line therapy. There were also cautions that this is not a curative therapy and many patients will not respond.

Long-term responders

The sponsor has retrospectively defined and identified a subpopulation of patients with long-term responses. The sponsor defined these patients according to the following criteria

- **Achieved a CR, CCR or PR to the TTR**
- **The time to progression (from study entry) was at least one year**

These criteria were not prospectively discussed or agreed upon with FDA and the sponsor has provided no clear rationale or justification for these criteria based upon literature review or other sources. The 76 patients meeting these criteria constitute two-thirds of all patients who have responded to the TTR. The FDA has further segregated this subset into 68 patients who received the dose and schedule for which marketing approval is being sought and 8 patients who received a different dose and schedule. The efficacy results in these subsets are summarized in the following table:

Efficacy Outcome	Patients without long-term responses	Corixa Long-term Responder Dataset	Single Dose Long-term Responders Per FDA	Multiple Dose Long-term Responders Per FDA
Number of subjects	n=193	n=76	n=68	n=8
Response				
CR (%)	13 (7%)	30 (39%)	30 (44%)	
CCR (%)	2 (1%)	28 (37%)	24 (35%)	4 (50%)
PR (%)	49 (25%)	18 (24%)	14 (21%)	4 (50%)

3. **Does the finding of a subpopulation of patients with long-term responses demonstrate that the TTR provides meaningful therapeutic benefit to patients over existing treatments (e.g., improved patient response over available therapy)?**

No vote was taken on this question.

The Committee stressed that this treatment is a form of specifically-delivered radiotherapy, and although some clinical benefit can be seen, it is not clear that there is benefit over existing available therapy, as there were no studies of appropriate design for making these comparisons.

Additional studies

4. **Please comment on the types of information that should obtained in additional studies to further characterize the safety and effectiveness of the tositumomab therapeutic regimen. Specifically, comment on the following:**

   - **The sponsor has proposed a trial of Rituximab vs. the TTR in patients with NHL who have received at least one and no more than two prior chemotherapy regimens. The primary objective of this trial is demonstration of a longer time to progression, alternative therapy, or death in TTR-treated patients. Survival is a secondary objective.**

   - **Please comment on the need to conduct studies to further assess delayed toxicities, including MDS/ secondary malignancies, hypothyroidism, and HAMA.**

   The Committee would like to see studies directly comparing this treatment to Zevalin, studies on the interactions with concomitant medications, and broader studies with longer more than 5 years, more careful follow-up. Quality of Life studies, including the impact of the treatment on the families and caregivers, were suggested. Eligibility criteria must consider the toxicity profile, e.g., asymptomatic patients with very localized disease should not be included, due to the risk of toxicity.

   HAMA information should be clearly explained, as a positive HAMA status will alter future diagnostic studies using murine antibodies, and also alter the distribution of future treatment involving murine antibodies.

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NDA 20-498, S012, CASODEX® (150 mg bicalutamide), AstraZeneca Pharmaceuticals LP

- indicated as (1) adjuvant therapy to radical prostatectomy and radiotherapy of curative intent in patients with locally advanced non-metastatic prostate cancer who have a high risk for disease recurrence or (2) immediate treatment of localized non-metastatic prostate cancer in patients for whom therapy of curative intent is not indicated

Open Public Hearing

Bob Samuels – Florida Prostate Cancer Network, Inc.
Anthony A. Caputi, Jr. – American Foundation for Urologic Disease
Jan Marfyak – Pennsylvania Prostate Cancer Coalition
Merel Grey Nissenberg – California Prostate Cancer Coalition
John A. Page – Us Too! International, Inc.
Ben Fay – Wellness Community of Delaware

Sponsor Presentation	**AstraZeneca Pharmaceuticals LP**
Introduction and Regulatory History	Gerard T. Kennealey, M.D.
Need for CASODEX® in Early Prostate Cancer	Howard I. Scher, M.D. Memorial Sloan-Kettering Cancer Center

EPC Trial Program: Efficacy and Safety	William A. See, M.D. Medical College of Wisconsin
Relevance to Clinical Practice	Mark S. Soloway, M.D. University of Miami School of Medicine
Summary and Conclusions	Gerard T. Kennealey, M.D.

FDA Presentation

Background and Review Issues	Daniel Shames, M.D. Director, Division of Reproductive and Urologic Drug Products, FDA
Medical Review Findings	Scott Monroe, M.D. Medical Reviewer, FDA
Summary and Introduction of Questions	Daniel Shames, M.D.

Questions to the Committee

1. **Across ongoing Trials 24 and 25, only 15.6% of patients (Sponsor-preferred endpoints) and 9.3% of patients (FDA-requested endpoints) had objective progression of prostate cancer or died from any cause in the absence of disease progression. At the time of data cutoff (June 2000), median follow up was 2.6 years (Trial 24) and 3.0 years (Trial 25). In the absence of meaningful survival data or quality of life benefits, are these studies sufficiently mature to conclude with a reasonable level of confidence that patients treated with Casodex in these trials will derive clinically significant long-term benefit? If not, what additional information is needed?**

   YES – 3 ***N – 13***

   The Committee felt that the data suggest that there may be benefit for some patients in the United States, but it is unclear exactly who would be in this population. They felt that the data for true adjuvant use was not convincing, but that the drug might be appropriate for high risk patients identified post-surgically. The committee emphasized that prostate cancer is a disease with a very long natural history and that studies in this indication will require a very long follow-up (until the number of events is higher), and that survival benefits might not even be apparent at 15 years. PSA levels could be considered as an endpoint, as they are used clinically as an indicator of disease progression.

2. Do the data (clinical stages, PSA levels, and lack of valid Gleason scores) from Trials 24 and 25 allow for the adequate definition of a patient population that can be extrapolated from the non-U.S. studies to a defined group(s) of U.S. patients who will derive significant benefit from Casodex therapy?

   YES – 8 ***N – 8***

   The Committee felt that the European data from trials 24 and 25 do allow easy extrapolation to the U.S. population, as these patient groups represent a diminished population in the U.S. There may be some populations in the U.S. which are similar to those in the trials (men whose cancer is not identified by early screening, for example). These trials do provide evidence of efficacy in advanced disease, and might be useful for those who fail prostatectomy, as shown by a rapid PSA doubling, after surgery. A trial comparing Casodex, LHRH agonists and placebo post-surgery or radiation was suggested.

Because this disease does have such a long term course, it is difficult to accept intermediate endpoints of questionable value. Drugs must have clear and specific instructions for use in an appropriate population.

3. Based on the findings in Trial 23 as of the June 2000 data cutoff, it appears that Casodex does not offer a significant benefit for men with early prostate cancer who initially are treated by radical prostatectomy or radiation therapy with a curative intent. In light of this observation:
   a) What population of patients, if any, who are initially treated by radical prostatectomy or radiation therapy of curative intent in the U.S., would benefit from adjuvant treatment with Casodex?

      Trials with longer follow-up are necessary before such a population can be identified.

   b) If you have identified a population that you believe would derive clinically significant benefit, what are the data in the Sponsor's submission that support your recommendation? Please identify
      1. The specific study(s) and patient population(s).
      2. The specific benefits and risks for this population.
      3. Any additional need for data (be specific)

   c) If you were unable to identify a population, what additional data would you require to allow you to conclude that Casodex adjuvant would provide a clinically significant benefit for U.S. patients?

      The Committee felt that the high-risk population would be important to study, and that patients treated with radiation may benefit. They would like to see the inclusion of endpoints involving quality of life, and the delay of metastatic disease.

4. In the U.S. Trial (Trial 23), there was no watchful waiting (surveillance) treatment group.
   a) Has the Sponsor demonstrated in Trials 24 and 25 (both non-U.S. trials) that U.S. patients with localized non-metastatic prostate cancer who are presently managed by surveillance (i.e., watchful waiting) would derive sufficient benefit from Casodex monotherapy or immediate treatment to justify the adverse events that would be associated with such treatment?

   b) If you answered "yes"
      1. What are the data that support your decision?
      2. What are the characteristics of the U.S. patients who would derive benefit?
      3. What are the specific benefits and risks for these patients?

   c) If you answered "no"
      1. What additional data would you require to allow you to conclude that Casodex monotherapy would provided clinically significant benefit for U.S. patients presently managed by watchful waiting?

      These questions were addressed as a whole. The Committee indicated that trials 24 and 25 represent a population not frequently seen in the United States. In the U.S., those treated by "watchful waiting" have low risk disease and these are also the people least likely to benefit from Casodex 150 treatment. There is a population who elects to have neither surgery nor radical prostatectomy, but do show disease progression as indicated by rapidly rising PSA levels, but it is very small.

      It was emphasized that there are significant differences between the current U.S. population and the population of Europe. Men in the United States are much more likely to have their disease identified early, by routine screening procedures. (The men in the Scandinavian study were symptomatic, as screening was not routinely practiced there at the time of the study.) In summary, trials 24 and 25 represent a population not frequently seen in the U.S., and trial 23 did not show clear clinical benefit.