BLA Reference number 99-0786
Product: CAMPATH
Sponsor: Millenium

Proposed Indication: "for the treatment of patients with chronic lymphocytic leukemia who have been treated with alkylating agents and who have failed fludarabine therapy"

1. In the primary efficacy study conducted in 93 patients with fludarabine-refractory CLL, an overall response rate of 33% (95% confidence interval 23%, 42%) was observed with a CR rate of 2%. The median duration of response was 6.9 months, with 7 of the 93 patients (8%) experiencing a response lasting greater than one year. The overall response rates in two smaller studies conducted in a similar, though less heavily pre-treated, population were 29% and 21% and the median duration of response in these studies was also similar. Due to the lack of a control group, one cannot determine whether specific patient benefits occurred. There was improvement in "B" symptoms in the one-third of responding patients who were symptomatic at study entry, however the requirement for blood product transfusion and the incidence of infection, two important manifestations of CLL, appeared to worsen on study.

   FDA stated in guidance that for refractory malignancies (i.e., those for which no effective alternatives existed), reduction in tumor volume may serve as a surrogate for clinical benefit.[1, 2] The association of this surrogate (reduction in tumor) with patient benefit is stronger when the tumor is reduced to undetectable amounts (complete response) and when the reduction in tumor is durable and extends beyond the period when toxic agents are being administered.

   Please discuss whether, for patients with fludarabine-refractory CLL, the response rate, duration of response and clinical outcomes observed in these studies are reasonably likely to predict clinical benefit?

2. All three studies presented are uncontrolled, single arm studies. In any study it is difficult to determine the causal relationship of an adverse experience to the study drug, other interventions, and underlying disease. However, in an uncontrolled (single arm) study, one also loses the ability to assess for relative differences in toxicity between treatment groups. In the primary efficacy study, the toxicity profile of CAMPATH was characterized as follows:

- 90% of patients experienced infusional toxicity; 13% grade 3-4, despite premedication and a gradual dose escalation.
- 47% of patients required an interruption of therapy; 32% required an interruption of therapy for one week or greater (these patients needed to re-escalate to the effective dose).
- 24% of patients discontinued treatment for adverse events and an additional 4% refused to continue.
- 67% of patients experienced serious adverse experiences, characterized as infusional, infectious, or hematologic toxicity; the latter two were often inter-related.

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[1] Guidance for Industry: Providing Clinical Evidence for Effectiveness for Human Drug and Biological Products (Oncology Supplement) May 1998
[2] Reinventing the Regulation of Cancer Drugs March 1996

- 15% of patients died, possibly or probably from toxicities related to CAMPATH. In the absence of a well controlled trial, the impact of CAMPATH on overall survival cannot be determined.

Hematologic toxicities

- 47% of patients experienced grade 3-4 anemia; 50 transfusion-independent patients required PRBC transfusions and received a median of 6 units.
- 24% experienced grade 3 and 55% grade 4 neutropenia; two months following the last dose of drug, 38% of patients had not recovered to baseline neutrophil counts.
- 94% experienced grade 3 and 18% grade 4 thrombocytopenia; 50 transfusion-independent patients required transfusions and received platelets on a median of 3 separate times. One patient died as a result of refractory thrombocytopenia.
- Aplastic anemia was noted in earlier studies in patients with NHL. There was a striking rise in incidence at cumulative weekly doses of ≥240 mg for more than 2 weeks. 5 patients experienced profound pancytopenia and 3 patients died prior to hematologic recovery.

Immunosuppression/Infectious toxicities

- CD4 counts were profoundly decreased at the end of 4 weeks of CAMPATH therapy and had not recovered to baseline 6 months post-treatment.
- 54% (62 of 115) of the serious adverse events were infectious in nature and included 29 episodes of opportunistic infection (25% of SAEs) and 16 episodes of febrile neutropenia (14% of SAEs), despite Bactrim/Acyclovir prophylaxis.
- Among the 30 deaths that occurred in the 6 months following initiation of CAMPATH, approximately half were infectious and generally occurred in association with cytopenias.

Is the toxicity profile of CAMPATH acceptable in light of the benefit that may be conferred?

3. If CAMPATH receives accelerated approval, please discuss the types of confirmatory studies that should be conducted. Among these, please comment on the following study designs:

- Millenium proposed Phase 4 study: Multicenter, randomized study of CAMPATH (vs. no additional therapy) in patients who have achieved a CR or PR to fludarabine therapy

- FDA recommended Phase 4 study: Multicenter, randomized study of fludarabine vs. CAMPATH in patients with CLL who have not yet received fludarabine

- Multicenter, randomized study of CAMPATH vs supportive care (no additional therapy) in patients who have failed fludarabine.

Please comment on the preferred primary study endpoint (e.g., survival, progression-free survival). Please comment on the acceptability of the criteria for progression proposed by Millenium vs. the NCI WG criteria.