

## Charles Morris, MD, VP Clinical Research, Cephalon

Now in its twentieth year of business, Cephalon started as a small biotech company in 1987 and has grown into a full-fledged international biopharmaceutical company. With offices in the US and Europe, Cephalon employs approximately 3000 people. On the advent of the

FDA's approval of Treanda®—the first cancer drug for 2008—for the treatment of chronic lymphocytic leukemia (CLL) we conducted an interview with Charles Morris, MD, Vice President of Clinical Research, Cephalon. Following is an excerpt from that interview.

**OBR:** We've been hearing a lot at the various medical meetings about Treanda® and now we have an FDA approval. Congratulations. What is the background on Treanda?

**CM:** Treanda [bendamustine HCl] is a new cytotoxic agent that was originally discovered in the former East Germany where it was being used since the 1970s for a number of hematologic malignancies. In early 2000, after publication of several clinical studies in Germany, Treanda captured the attention of US researchers. We acquired US rights to the compound and thereafter began several investigational clinical studies on the compound.

In September 2007, we completed our new drug application [NDA] for patients with chronic lymphocytic leukemia (CLL) and the FDA subsequently granted us a priority review of the NDA. We also have been fortunate to receive Orphan Drug status for Treanda as a CLL treatment. In December 2007, we also submitted an NDA for the treatment of patients with relapsed indolent B-cell non-Hodgkin's lymphoma who have progressed during or following treatment with rituximab or a rituximab-containing regimen. We are seeking approval on that NDA from the FDA later this year, around October.

**OBR:** Can you explain a little bit of what Treanda actually is and how it works?

**CM:** Treanda is actually a hybrid in structure. What I mean by that is that structurally it is in part an alkylating agent and in part a purine analog. We don't fully understand the mechanism of action of Treanda, but we know it leads to cell death via two different pathways: by damaging the DNA in cancer cells resulting in apoptosis; and by disrupting normal cell division which then leads to mitotic catastrophe. The damage to the cancer cells caused by the drug is extensive and durable.

**OBR:** Tell us a little about the first-line CLL data presented at ASH '07, and how the new package insert reflects this data.

**CM:** The studies leading to approval of Treanda in CLL were conducted entirely in the European Union. In the randomized, international, multicenter, open-label, Phase 3 study, previously-untreated patients with B-Cell CLL [N=301] received either Treanda or chlorambucil. Both primary endpoints—overall response (i.e., reduction in blood counts, reduction in lymph node disease, and resolution of symptoms if they were present) and progression free survival—were met. Patients who received Treanda showed a longer PFS [18 months vs. 6 months] compared with those patients receiving chlorambucil. In addition, the Treanda patients showed higher overall response rates.

One of the assessments was overall response between the two groups. Statistical significance was shown for overall response (59% for the Treanda-treated patients vs. 26% for the chlorambucil-treated patients;  $P < 0.0001$ ). Furthermore, results showed that patients were more likely to get a sustained response from Treanda compared with chlorambucil.

**OBR:** What does the side effect profile of Treanda look like?

**CM:** As with any cytotoxic agent, the patterns for adverse events [AEs] with Treanda are typical. Most AEs—neutropenia, leukopenia, thrombocytopenia, and lymphopenia can be expected as a result of the MOA of the cytotoxic, but these side effects are not atypical. There are some grade 3 to 4 AEs—myelosuppression, infections, and infusion reactions, but nothing oncologists can't remedy and nothing that should prevent patients from continuing to receive treatment. We won't be recommending the drug to pregnant women.

**OBR:** The increase in remission rate was significant compared with chlorambucil, do you think we'll see an overall survival analysis from this study? If so, when can we expect that?

**CM:** The final analyses of the data will become available in June of this year. If there are trends in survival data, we



obviously will be able to pick those up, however the FDA has been prepared to use the PFS data for full approval.

**OBR:** Campath® was recently approved in the front-line setting for CLL also as a single agent. Do your clinical plans include comparing the safety and efficacy profiles of Treanda and Campath?

**CM:** As it stands now, no safety data exists for the two drugs and our priority is to learn more about Treanda as a single agent before launching into combinations. We're more interested in doing further studies in CLL and NHL with Treanda than we are in doing a head to head comparison with Campath. To be honest, nobody has suggested we do a study comparing Treanda to Campath. We'd rather focus our attention on the combination of Treanda with Rituxan® and see where that leads. A Phase 2 study in patients with relapsed indolent or mantle cell NHL we conducted in combination with Rituxan has produced favorable results with a manageable and tolerable side effect profile. We'd like to further investigate our findings and move to the next phase of this combination.

**OBR:** You mentioned mantle cell NHL. Are there any other tumor types in which you are studying Treanda?

**CM:** Our European partners are seeking indications in myeloma and solid tumors in addition to CLL and NHL. In mantle cell lymphoma, studies are showing high response rates so we're considering doing further studies in this patient population.

**OBR:** How soon do you anticipate Treanda will be made available for patients with CLL?

**CM:** As soon as possible. In April, 100 mg dose forms will be available along with reconstitution instructions.

**OBR:** Congratulations on the first NDA approval of '08 for a cancer indication. We trust you'll keep us updated on Treanda's performance in the marketplace.



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