NCCN Request For Proposals (RFP): Clinical Studies of Bendamustine in Solid Tumors

1.0 Purpose

The National Comprehensive Cancer Network (NCCN) has received a 1.2 Million Dollar research grant from Cephalon, Inc. (hereafter, “Grantor”) to support NCCN Member Institution faculty for the performance of clinical studies of bendamustine (Treanda®) in the treatment of solid tumors. NCCN will serve as the sponsor for these grants that are available only to NCCN investigators. The following details the objectives, process and requirements of this RFP.

2.0 Background

Bendamustine is an antineoplastic agent that was developed in the early 1960s by Ozegowski and Krebs at the Central Institute for Microbiological and Experimental Therapy in Germany (designated then as IMET 3393). Based on its unique chemical structure, the drug is best described as a purine analog/alkylator hybrid molecule. Specifically, the drug was synthesized with a benzimidazole ring situated in the center of its structure where it has been proposed a purine antimetabolite activity resides, and with a bifunctional mechlorethamine nitrogen mustard attached to the ring, which provides the alkylating properties.

The comprehensive mechanism of action for bendamustine in humans has not been fully characterized. The alkylating properties of the agent have been established and bendamustine induces apoptosis via single and double strand deoxyribonucleic acid (DNA) breaks. In addition, studies have concluded that bendamustine causes more extensive and durable DNA strand breaks than those seen with conventional alkylating agents.

In the NCI COMPARE analysis, bendamustine showed limited cross correlation with other alkylating agents. This analysis uses an algorithm to identify correlations among compounds in the NCI In vitro Cell Line Screening Project (IVCLSP). Common mechanisms of action between compounds are identified by a Pearson correlation coefficient (PCC) of > 0.8 which indicates a > 65% agreement in the sensitivity patterns of two compounds. When the NCI COMPARE analysis was conducted with bendamustine, the sensitivity pattern did not correlate with any of the compounds tested including conventional alkylating agents such as chlorambucil, cyclophosphamide and melphalan whereas the correlation coefficients among these three agents were strong (0.76-0.93). These results indicate that bendamustine has mechanism of action that goes beyond alkylation.

Bendamustine also appears to induce a non-apoptotic process of cell death called mitotic catastrophe. Mitotic catastrophe may occur in cells treated with bendamustine secondary to extensive and durable damage of DNA, coupled with the drugs inhibition of cell cycle progression enzymes, such as PLK-1 and Aurora Kinase A. When cells with extensive DNA damage enter mitosis, secondary to the inhibition of the mitotic checkpoints by bendamustine, this leads to mitotic catastrophe.
Bendamustine has been evaluated clinically in both solid tumors and hematological malignancies.

In Germany, bendamustine has been examined in the treatment of small cell lung cancer (SCLC). A phase II study of bendamustine in the second-line treatment setting with 21 relapsed SCLC patients demonstrated a response rate of 29%, all partial responders (PR) and median overall survival (OS) of 7 months. A follow-up study combining bendamustine with carboplatin in 55 previously untreated patients with extensive SCLC documented an overall response rate of 73% (1 complete response [CR], 39 PR, 14 stable disease [SD] and 1 progressive disease [PD]). These results indicate the drug has activity in SCLC, which warrants further investigation in combination with other chemotherapy and targeted therapies.

In addition, bendamustine has been tested in Germany as a treatment for breast cancer. A phase III multicenter randomized study compared bendamustine, methotrexate, and 5-fluorouracil (5-FU) (BMF) versus cyclophosphamide, methotrexate and 5-FU (CMF) as first line therapy in patients with metastatic breast cancer. The time to tumor progression (TTP) was significantly longer in the BMF group, 8.2 months versus 6.7 months (p=0.0071). A second non-randomized phase II study examined bendamustine alone or in combination with trastuzumab for HER2-positive patients with recurrent breast cancer that were previously treated with either anthracycline- or taxane-based chemotherapy. The overall response rate (ORR) was 18% with bendamustine alone in HER2-negative patients and 20% when combined with trastuzumab in HER2-positive patients. These results indicate that bendamustine has activity in breast cancer, which warrants further investigation in combination with other chemotherapy and targeted therapies in select populations.

Bendamustine has been extensively studied for hematological malignancies in both Europe and the United States (US). These studies have focused primarily on populations with chronic lymphocytic leukemia (CLL), non-Hodgkin’s lymphoma (NHL) and multiple myeloma.

In CLL a randomized trial of bendamustine vs. chlorambucil was conducted in patients with treatment-naïve disease. Results of this study showed a statistically significant improvement in ORR (62% vs. 33%); the CR rates were 27% vs. 2%, respectively. The median progression-free survival (PFS) for bendamustine was 21 months compared to 9 months for chlorambucil [hazard ratio (95% CI) 4.39 (2.58, 7.45) (p<0.0001)]. Based on these results Grantor submitted a new drug application (NDA) to the US FDA for bendamustine in the treatment of CLL. A decision on this application is expected on March 26th, 2008.

In NHL, three significant clinical trials have been completed in the US. A phase II single-agent multicenter study of bendamustine in rituximab-refractory indolent NHL (although 20% of the patients enrolled in this study had documented transformed disease). Results of this study showed an ORR of 77% (CR/CRu=34%, PR=43%, SD=4%, PD=17%), a median duration of response (DR) of 6.7 months and a median PFS of 7.1 months.

A pivotal phase III single-agent multicenter study of bendamustine in rituximab-refractory indolent NHL was also conducted. Results of this study showed an ORR of 75% (CR/CRu = 17%, PR=58%, SD=16%, PD=7%), a median DR of 9.2 months and a
median PFS of 9.3 months. Based on the results of this study, a second NDA for the
treatment of patients with indolent NHL who have progressed during or following
treatment with rituximab or a rituximab containing regimen was submitted in December
of 2007.

The third trial was a phase II study of bendamustine plus rituximab in relapsed indolent
and mantle cell NHL. This study showed an ORR of 92% (93% in indolent patients,
n=54; 92% in mantle cell patients, n=12), a median DR of 21 months and a median PFS
of 23 months.

Across all clinical trials, the toxicities from bendamustine have been predictable and
manageable. They include primarily myelosuppression as well as nausea and vomiting.
Alopecia is rare.

Four areas of research emphasis are identified for this RFP:
- Clinical studies examining the radiosensitizing potential of bendamustine;
- Clinical studies in CNS penetration of bendamustine;
- Clinical studies of bendamustine-based combination therapy in extensive small
cell lung cancer;
- Clinical studies of bendamustine in triple-negative breast cancer. Particular
emphasis will be placed on combination studies of bendamustine with targeted
biologic agents such as bevacizumab.

Studies with correlative endpoints are encouraged.

This program is designed to facilitate the implementation of new avenues of research in
the above areas of emphasis. Collaboration between NCCN institutions is strongly
encouraged in order to foster the interactive sharing of knowledge and expertise, and to
utilize the combined clinical strengths of members.

The NCCN Project Advisory Team (PAT) has developed a Request for Proposals (RFP)
with a formalized review procedure to accept applications and select the proposals of
highest scientific merit. The NCCN PAT has overseen the development of the RFP and
a NCCN Scientific Review Committee composed of some members of this group and
other NCCN clinical leaders will perform the review of applications.

3.0 Scope and Aims

This RFP seeks the submission of bendamustine-based studies in triple negative breast
cancer, extensive small cell lung cancer, with radiation as a sensitizer for treatment of
solid tumors, and in treatment of solid tumors involving the CNS. The overall aim is to
develop innovative studies to help determine the role of bendamustine in the treatment
of solid tumors. It is hoped proposals submitted in response to this RFP will be useful in
guiding further development of bendamustine. The following types of studies will be
accepted for review:

3.1 Clinical development of bendamustine in the treatment of solid tumors
involving the central nervous system (CNS). Studies will evaluate the
efficacy of bendamustine as a potential therapy for treatment of solid
tumors involving the CNS.
A. Evaluation of CNS penetration of bendamustine. These may include studies of bendamustine penetration into brain parenchyma or cerebrospinal fluid and may include:
   1. Clinical studies in humans with or without imaging;
   2. Evaluation of penetration of bendamustine.

3.2 Clinical development of bendamustine as a radiation sensitizing agent. Studies will evaluate bendamustine in conjunction with wide field radiation therapy in the treatment of solid tumors.
   A. Trials may focus on bendamustine and RT:
      1. Using bendamustine and RT alone:
         a. Phase I studies using standard bendamustine dosing with RT;
         b. Using alternative dosing schedules of bendamustine;
         c. Studies examining the effect of RT field size with toxicity;
      2. Using bendamustine and RT with radiation sensitizing chemotherapy agents;
   B. Objectives of the study may include, but are not limited to:
      1. safety/toxicity
      2. efficacy
      3. quality of life

3.3 Clinical studies of bendamustine in treatment of triple negative breast cancer may include the following:
   A. Single-arm Phase II or randomized Phase II Trials evaluating the potential efficacy of bendamustine in the treatment of triple negative breast cancer:
      1. Bendamustine alone;
      2. Phase I/II studies of bendamustine in combination with other conventional chemotherapy agents or targeted biologic agents;
   B. Laboratory correlates of activity of bendamustine.

3.4 Clinical studies of bendamustine in treatment of small cell lung cancer may include the following:
   A. Single-arm Phase II or randomized Phase II Trials evaluating the potential efficacy of bendamustine in the treatment of small cell lung cancer:
      1. Bendamustine alone;
      2. Phase I/II studies of bendamustine in combination with other conventional chemotherapy agents or targeted biologic agents;
   B. Laboratory correlates of activity of bendamustine.
4.0 Study Time Frames

All approved studies are expected to commence within six (6) to nine (9) months of notice of approval.

Larger Randomized Phase II multi-institutional studies with an estimated three-year completion rate. Multi-institutional data management and monitoring of these studies should be coordinated by the lead institution. Additional funding for the lead institution may be requested to support the additional resources required for this activity.

Single-arm Phase II studies are expected to explore new approaches that can be tested in larger confirmatory studies if positive results are obtained. It is expected that these studies will be completed in 12-18 months. To meet this accrual goal, single-arm Phase II trials may be multi-institutional. Data management and monitoring of studies should be coordinated by the applying institution. Additional funding for the lead institution may be requested to support the additional resources required for this activity, if the study involves multi-institutional participation.

Phase I and smaller Single-arm Phase II studies are expected to explore new approaches that can be tested in larger confirmatory studies if positive results are obtained. It is expected that these studies will be completed in 12-18 months.

Correlative laboratory studies are expected to be completed within the same time frame as the corresponding clinical trial. Laboratory studies accompanying an ongoing Cooperative Group trial are permissible.

All studies will require documentation of the feasibility of accruing the targeted study population and all studies may be multi-institutional.

5.0 Proposals

In order to respond to the RFP, investigators will submit a proposal in the format delineated in Section 5 below to NCCN, which will be evaluated by the NCCN Scientific Review Committee.

Proposals will provide concise documentation of the research plan and are to be modeled after the NCI Letter of Intent. The proposal is expected to contain sufficient information to allow the reviewers to fully assess the scientific rigor of the proposed study. A full protocol may be submitted as an attachment to a proposal.

The budget should be developed using the NCI Budget Template and contain justification for the major categories. The proposal should describe the following areas:

5.1 Clinical Trials (Maximum 5 Pages)
A. Title/Tumor Type
B. Investigators and institutional affiliations
C. Hypothesis/objectives
D. Research design
E. Study population
   i. Stage
   ii. Major inclusions/exclusions
F. Treatment plan
G. Endpoints/Statistical analysis
H. Feasibility
   i. Estimated time of completion/monthly accrual
   ii. Previous experience
   iii. Collaborators’ experience including affiliates
i. If correlative studies are proposed, maximum additional 3 pages

5.2 Budget (Maximum 3 Pages) - Must use NCI Budget Template
A. Breakdown by major cost categories.
B. Justification of major costs with enough detail to demonstrate how funding for major elements in the study will be allocated.
C. For combined clinical and correlative studies, separate budgets for each component should be submitted.

5.3 Ancillary Documentation
A. An NCI format BioSketch of the Principal Investigator
B. An appendix of supportive literature may be provided

6.0 Proposal Requirements

6.1 Submission

All proposals must be submitted electronically to Hampton@nccn.org and are due to the NCCN office by close of business, 5:00 PM (EDT) on Friday, April 11, 2008.

For questions or issues, please call Debra Hampton at (215) 690-0230. NCCN will seek to provide information to potential investigators regarding ongoing or completed studies of bendamustine.

6.2 Requirements

6.2.1 Human Biological Specimens – All specimens must have been obtained under informed consent and IRB approval appropriate for the study. A letter of assurance must be provided to NCCN that the PI’s academic institution owns and has full rights to the tissue without conflicting claims from a non-Grantor commercial entity. Compliance with all federal regulations is required.

6.2.2 IRB:

   6.2.2(a) All investigators will submit protocols for IRB review and document approval to NCCN prior to study activation and all collaborators will furnish evidence of IRB approval. It is expected that IRB review and approval be completed within 90 days following NCCN notification of funding for the project.

   6.2.2(b) Protocols will be reviewed by NCCN for consistency with approved proposals prior to IRB review. Copies must be submitted to NCCN at least 1 week prior to IRB submission.
6.2.2(c) IRB approval documents must be submitted to NCCN prior to study activation and all collaborators will also furnish evidence of IRB approval.

6.2.3 Investigator will register the Study with the clinical trials registry, www.clinicaltrials.gov, within twenty-one (21) days of the date enrollment is opened, irrespective of whether the Study involves an IND or an IND exempt clinical trial.

6.2.4 Serious Adverse Event Reporting: All adverse events will be reported to the FDA in accordance with FDA requirements and to the Grantor.

6.2.5 Institutional Monitoring: All studies will be internally monitored in accordance with appropriate committees (e.g. institutional Data Safety and Monitoring Plan in the case of human studies).

6.2.6 IND:

6.2.6(a) Investigators are encouraged to apply to the FDA for IND exemption if studies meet all criteria according to 21 CFR 312.2(b). A copy of the FDA approval letter for IND exemption must be submitted to NCCN before study drug will be released. If exemption is not approved, investigators are required to hold INDs for studies but will be allowed to cross-reference a filing to Grantor’s IND.

6.2.6(b) If bendamustine is studied in combination with an IND agent from another pharmaceutical company, or an agent used outside of its indication, the investigator must provide documentation of that company’s commitment to provide drug for the investigation as well as the agreement of that company to allow presentation of results. **This documentation must be provided to NCCN along with the proposal.**

6.2.6(c) Proposals using an experimental diagnostic imaging agent that will require an IND must outline how regulatory issues will be handled in order to meet the required study time frame.

6.2.7 Progress Reports: Investigators will provide interim progress reports to NCCN detailing the progress of studies quarterly, and upon study completion. These reports will be used administratively for funding purposes. If study progress or accrual lags behind the expected rate, the NCCN Scientific Review Committee (SRC) may be asked for suggestions to improve study progress, or alternatively, to terminate the study and any further funding.

6.2.8 Specimen Transmittal: If specimens are to be transported extramurally for collaborative laboratory studies, all institutional requirements for safety and confidentiality will be met.
6.2.9 **Investigators Meeting:** All studies will be presented by institutional representatives at an annual NCCN investigator meeting. The purpose of this meeting will be to discuss preliminary results and develop new research initiatives and further collaborative activities between NCCN investigators and the Grantor scientific staff. Separate funds will be provided by Grantor for attendance at this meeting. Participation by the PIs in these meetings is a requirement of a funded study.

6.2.10 **Abstracts and Publications:** Abstracts for presentation at scientific meetings and all publications of study results will be submitted to NCCN and Grantor for review related to protection of company's intellectual property and confidential information **prior to any submission.** Abstracts must be submitted at least 10 days prior to submission and manuscripts at least 30 days prior to submission. Grantor may delay publication and disclosure of the manuscript or abstract for up to an additional sixty (60) days so as to seek patent protection of intellectual property rights.

6.2.11 **NCCN Multi-Institutional Studies:** Collaborative studies between NCCN member institutions are encouraged. For these studies, the proposal feasibility section should provide information about data management and, if relevant, specimen handling issues. Additional funding may be provided for centralized data management and monitoring by the lead institution.

6.2.12 **NCCN institutions and investigators will be responsible for conducting all studies in accordance with the applicable research plan, GCP Guidelines, and all applicable laws and regulations.** NCCN institutions and investigators will be responsible for all data collection, statistical analysis and safety reporting.

6.2.13 **Final protocols must be consistent with approved proposals. Funds will be rescinded if there are significant changes without prior NCCN approval. There will be no exceptions.**

7.0 **Drug Supply**

Grantor will supply bendamustine for all approved and funded studies.

8.0 **Selection Criteria**

Proposals will be judged by the NCCN Scientific Review Committee based on the following criteria:

1. Scientific value;
2. Soundness of study design;
3. Feasibility including reasonable assurance of achieving intended and full accrual;
4. Budgetary reasonableness;
5. Expected applicability in the evaluation of and the appropriate use of bendamustine in solid tumors.
9.0 Funding

NCCN and its member institutions have an agreement to include a maximum of 25% indirect costs for trials funded by the NCCN. Direct funding will include all costs including investigators’ salaries. For example, $80,000 direct costs, $20,000 indirect costs for a total grant of $100,000.

Multi-center Randomized Phase II studies will be funded up to a cost of $500,000 (total costs including direct costs and 25% indirect costs) per trial. Per patient costs will not exceed $5,000 per patient. Additional funding will be considered for data management and monitoring for multi-center trials. These funds should be delegated at the discretion of the lead investigator and may include outsourcing of data management and/or monitoring to an independent research organization.

Phase I and Single-arm Phase II clinical trials will be funded at a cost of up to $200,000 (total costs including direct costs and 25% indirect costs) per trial. Per patient costs will not exceed $5,000 per patient. In the case of a multi-centered, single-arm Phase II trial, additional funding will be considered for data management and monitoring. These funds should be delegated at the discretion of the lead investigator and may include outsourcing of data management and/or monitoring to an independent research organization.

The Correlative Laboratory studies section of the clinical trial will be funded up to a total cost of $100,000, including up to 25% indirect costs.

Phase II trials and correlative studies will have funding awarded on the following schedule:

- 25% after IRB approval and implementation
- 35% after 50% accrual
- 30% after 100% accrual
- 10% after submission of a manuscript for publication

Phase I trial funding will be awarded on the following schedule:

- 25% after IRB approval and implementation.
- Based on the per patient costs, after the initial 25% of funding has been accounted for based on patient accrual, funds will be awarded on a quarterly basis for eligible patients enrolled on study, based on the per patient rate up to a maximum of 90% of funds.
- 10% of funds will be awarded after submission of a manuscript for publication.

The goal is to have rapid submission of a manuscript so as to have the data available to the wider scientific community.

Studies that do not meet the time frame requirements as stipulated in Section 4.0 will have funds rescinded and will be required to return any and all funds previously disbursed.
10.0 Study Agreement

A study agreement will be signed between NCCN and each participating institution.

If an institution requires a separate contract with another pharmaceutical company for a study approved and supported under this RFP, that contract must be fully executed by the time of final contract execution with NCCN.

All aforementioned points between NCCN and the participating institution must be strictly adhered to.