April 5, 2013

Joan S.McClure, MS
Senior Vice President of Clinical Information and Publications
National Comprehensive Cancer Network
500 Old York Road, Suite 250
Jenkintown, PA 19046

RE: NCCN Compendia Review

Dear Ms. McClure:

Per our conversation, I am submitting this request for the NCCN compendia to review the enclosed data for the inclusion of Erwinia Asparaginase (Erwinia) to be noted as a first line treatment for ALL and to allow for IM and IV routes of administration.

Specific Changes:

Currently Erwinia Asparaginase is included in the NCCN Guidelines, but as a treatment regimen for Asparaginase Toxicity Management. We are seeking expansion of Erwinia Asparaginase to be an initial ALL therapy, replacing the current E Coli Asparaginase (ELSPAR) indications. COG has already made these modifications and we are requesting that the NCCN guidelines incorporate these changes in its ALL treatment guidelines. In addition, we are requesting inclusion of intravenous as well as intramuscular treatments, to support common practices.

Rationale:

Lundbeck, the sole manufacturer and distributer of E. coli Asparaginase (Elspar ®) in the United States, recently informed the FDA that they plan to discontinue production and distribution of this agent and it is no longer available as of December 2012 in some areas. This agent is utilized in several COG ALL and AML studies. COG has selected Erwinaze as the replacement for Elspar (below are recommendations from COG for the replacement of Elspar in these studies if it is unavailable). Some of the ELSPAR indications are off label for Erwinaze, however, so there is a concern that as Erwinaze is placed into first line treatment, providers may experience some problems in getting reimbursed for its use. We are seeking a compendia change from the ALL panel to expand the use of Erwinia for these off label indications in order to ensure accessibility of Erwinia Asparaginase (Erwinia) when E. Coli Asparaginase (Elspar®) is no longer available.

AALL0631:

The AALL0631 Induction is the same for all patients, with dose modifications based on age, and includes E. coli Asparaginase. If E. coli Asparaginase is unavailable, it should be replaced with

Erwinia Asparaginase following the schedule and dose reductions as per AALL0631 Section 4.4: "All patients will receive the same Induction chemotherapy with regard to agents and schedule; however, patients ≥ 7 days and < 6 months old at diagnosis will receive an 11% dose reduction for all non-intrathecal agents (see Section 4.4.2 below) and patients < 7 days old at diagnosis will receive an additional 25% dose reduction for all non-intrathecal agents

> *Induction therapy doses:*
> *For ≥ 6 months at diagnosis: 30,000 IU/m2/dose intramuscularly (IM) days 15, 18, 22, 25, 29 and 33*
>
> *For ≥ 7 days - < 6 months at diagnosis: 27,000 IU/m2/dose IM days 15, 18, 22, 25, 29 and 33*
>
> *For < 7 days at diagnosis: 20,000 IU/m2/dose IM Days 15, 18, 22, 25, 29 and 33*
>
> *If allergy to Erwinia asparaginase develops, no further Asparaginase should be administered during Induction.*
>
> *Post-Induction therapy: Patients should receive PEG Asparaginase as currently stated in the protocol. If allergy to PEG asparaginase develops, the patient should receive Erwinia asparaginase at doses described in Section 5.1: "The FDA approved Erwinia asparaginase for use following allergy to pegaspargase, with a dose of Erwinia 25,000 IU/m2 x 6 doses IM on a Monday/Wednesday/Friday schedule substituted for a single dose of pegaspargase."*

Intensively Timed High-Dose Cytarabine + E. coli Asparaginase ("Capizzi-II"):
AALL0433: Induction 3
AALL07P1: Re-Induction Block 3
AAML1031: Intensification II, Arms A&B High Risk Patients

If E. coli Asparaginase is unavailable, it should be replaced with Erwinia asparaginase. The suggested replacement dose/schedule is Erwinia 25,000 IU/m2 every other day for two doses, beginning at hour 42, to replace each dose of E. coli asparaginase. If Erwinia asparaginase is not available, pegaspargase should NOT be given. Rather, all asparaginase should be omitted during the phase.

Common oncology practices support giving Erwinia Asparaginase both intramuscular and intravenously. Both routes of administration should be included in the guidelines to provide the oncologist selection of the favored mode of administration and to ensure reimbursement regardless of the method chosen. As one of the primary users, Bill Greene, the Chief Pharmaceutical Officer at St. Jude Children's Research Hospital, informed us that the primary route of administration they use is IV. Mr. Greene also stated that he would be pleased to provide information on how to dose asparaginase by the IV route if the committee desires, so please notify us if you would like his contact information.

The following articles are submitted in support of this proposed change:

1. National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Acute Lymphoblastic Leukemia, Version 1.2012. Current guidelines for reference purposes.

2. Children's Oncology Group, Memo Dated September 24, 2012, Availability of E. coli Asparaginase (Elspar®)) and use of Alternative Asparaginase Products in COB ALL and AML Trials. COG recommendations for expansion of Elspar indications to replace alternative Asparaginase products in current and ongoing trials.

3. Pieters, R, et al L-Asparaginase Treatment in Acute Lymphoblastic Leukemia, *Cancer Month 00,2010; 000:000-000*. Addresses the safety profile of Erwinia asparaginase and the recommendation that administration be either the IV or IM route.

4. Pidaparti, M and Bostrom, B., Comparison of Allergic Reactions to Pegasparaginase Given Intravenously Versus Intramuscularly, *Pediatr Blood Cancer* DOI 10.1002/pbc.23380. Analysis of the risks and safety profile of IM and IV administration of pegasparaginase.

Please let me know if you require additional information regarding this request.

Sincerely,

George Whitelaw
President
SMT, Inc.
Suite 106
1129 Broad Street
Shrewsbury, NJ 07702
Phone: 732-935-3535
Email: gnw@smt-inc.net

Enclosures